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VOLUME 41

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ERRATA

Volume 41, Number 1, August, 1947

Page 110: The boiling point for $(n\text{-}C_3H_7)_3SiH$ in Table 3 should read 170-1° instead of 107-1°.

Page 128: n_D for $[(C_2H_5)_3Si]_2O$ in the first line of Table 9 should read 1.4340 instead of 41.430.

Page 137: In the fourth line of Section IX change "of the red blood cells" to read "on the red blood cells".

ERRATA

Volume 40, Number 3, June, 1947

Pages 365 and 378: Substitute "Coonradt" for "Coonvadt".

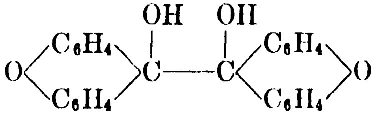
Volume 41, Number 1, August, 1947

Page 51: At the top of the ring in the formula at the extreme right of the second equation substitute "C" for "O".

ERRATA

Volume 40, Number 2, April, 1947

Page 182: The first formula in the equation in Section A should be:



Page 193: In formula XXXIXa delete the H on the right-hand side of the lower carbon atom.

Page 194: In formula XLa delete the H on the right-hand side of the lower carbon atom.

In formula XLIa delete the H on the right-hand side of the second carbon atom.

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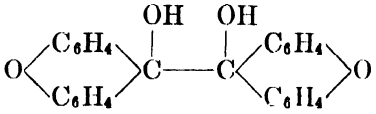
ERRATA

Volume 40, Number 2, April, 1947

Page 182: The first formula in the equation in Section A should be:



Page 193: In formula XXXIXa delete the H on the right-hand side of the lower carbon atom.

Page 194: In formula XLa delete the H on the right-hand side of the lower carbon atom.

In formula XLIa delete the H on the right-hand side of the second carbon atom.

THE CHEMISTRY OF THE TETRAZOLES

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Remington Rand Inc., South Norwalk, Connecticut

Received February 18, 1947

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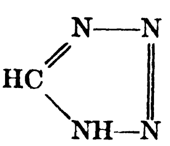
I. INTRODUCTION

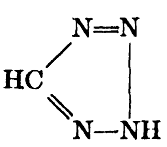
Although the tetrazoles have been extensively investigated, and well over 300 members of this class of nitrogen heterocycles have been prepared, there has been no recent comprehensive review of their chemistry. The section in the textbook by Meyer and Jacobsen (71), published in 1923, is the most complete summary of this group of compounds available. Knowledge of the tetrazoles, however, has been considerably increased since that time.

The present survey reviews the chemistry of tetrazole and its mono- and disubstituted derivatives. Tetrazolium salts and various reduced tetrazoles which have been described from time to time will not be discussed, except in so far as they may form the starting point for the synthesis of tetrazoles.

The tetrazoles are characterized by a five-membered, doubly unsaturated ring consisting of one carbon and four nitrogen atoms. Tetrazole itself may exist in the tautomeric forms I and II, the position of the hydrogen atom attached to nitrogen being indeterminate.



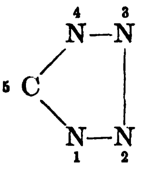
I



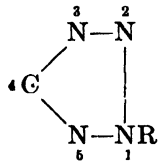
II

Linlithgow Library.

Mono- and di-substituted derivatives of both forms are known. Furthermore, the tetrazole ring may form part of a fused-ring system. The simplest numbering scheme for the tetrazoles is

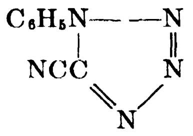


although an alternative system was used in *Chemical Abstracts* for derivatives of formula II prior to 1937.



The system mentioned first will be used throughout this discussion for the sake of consistency and to avoid confusion.

The first tetrazole was prepared in 1885 by the Swedish chemist, J. A. Bladin, at the University of Upsala during the course of an investigation of the reactions of dicyanophenylhydrazine, the condensation product of cyanogen and phenylhydrazine. Bladin observed (5) that the action of nitrous acid on dicyanophenylhydrazine led to the formation of a compound, $C_8H_5N_5$, to which he ascribed the formula:

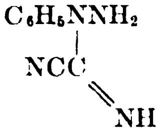


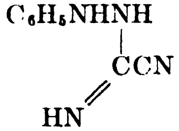
Hydrolysis, followed by decarboxylation, produced a compound having the formula $C_7H_6N_4$, the $C_6H_5CN_4$ unit remaining intact throughout these transformations (6). During his study of dicyanophenylhydrazine, Bladin had prepared numerous triazoles, and the possibility of forming a nitrogen heterocycle with one more ring nitrogen was a logical extension of his interpretations. The following year Bladin proposed the name "tetrazole" for the new ring structure (7) and in 1892 succeeded in preparing tetrazole itself by the following series of reactions (10), starting with the carboxylic acid produced from his phenylcyanotetrazole.

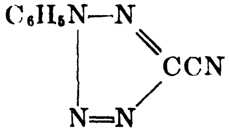
$$\begin{tikzcd}
\text{Phenyltetrazolecarboxylic acid} \arrow[r, "HNO_3"] & \text{Nitrophenyltetrazolecarboxylic acid} \arrow[d, "SnCl_2"] \\
\text{Tetrazole} \atop CH_2N_4 & \text{Aminophenyltetrazolecarboxylic acid} \arrow[l, "KMnO_4"']
\end{tikzcd}$$

It thus became evident that the ring system with one carbon and four nitrogen atoms was capable of withstanding a variety of chemical agents, and was possessed of considerable stability. Bladin summarized his work in an extensive review (11) and thereafter discontinued his investigations in this field.

It was subsequently shown by Bamberger and De Gruyter (2) and by Widman (146) that Bladin had assigned an incorrect formula to dicyanophenylhydrazine, with resultant error in the structural formulas for many of the triazoles and tetrazoles derived therefrom. Comparison of Bladin's formula for dicyanophenylhydrazine with that shown to be correct by Bamberger and De Gruyter reveals that cyanophenyltetrazole must have the structure of a 2,5-disubstituted tetrazole.


Formula of Bladin


Formula of Bamberger and De Gruyter


Cyanophenyltetrazole

Dicyanophenylhydrazine

Following Bladin's work the investigations in tetrazole chemistry became more numerous. The studies of 5-aminotetrazole by Thiele (135) and coworkers (139, 140), those on the 5-arylsubstituted tetrazoles by Pinner (91) and by Lossen and his group (64, 65, 66, 67), and those on sulfur derivatives of tetrazole by Freund and Paradies (39) were outstanding in the early period, and provided a basis for later extensions. In 1910 the simplest synthesis of tetrazole was achieved by Dimroth and Fester (30) by the direct combination of hydrogen cyanide and hydrazoic acid. The numerous papers by E. Oliveri-Mandalà and his collaborators describe a variety of tetrazoles. Oliveri-Mandalà is one of the few investigators who has studied the acidic and basic dissociation constants of tetrazole derivatives (74).

The most prolific modern investigator of tetrazoles has been R. Stollé of Heidelberg, whose studies of this class of heterocycles occupied the period 1914–1937. His investigations touched on every aspect of this field, and he filled innumerable gaps in the knowledge of these compounds. Mention should be made of the work of K. F. Schmidt (101), whose discovery of the interaction of hydrazoic acid and carbonyl compounds in the presence of acid catalysts has been widely applied to the synthesis of tetrazoles. In particular it has led to the synthesis of pentamethylenetetrazole, better known as metrazole. Although exceedingly few investigations of the tetrazoles have been made by Americans, an interesting description of these and other five-membered heterocycles in terms of the nitrogen system of compounds has been given by Franklin and Bergstrom (37).

II. Physicochemical, Physical, and Explosive Properties of the Tetrazoles

The comparatively small number of dissociation constants for tetrazole derivatives which have been measured are listed in table 1. These are due largely to Oliveri-Mandalà. The acidic dissociation constants were obtained by means of conductivity measurements, while the hydrolysis constants of the *N*-substituted tetrazole hydrochlorides were determined from the influence of these substances on the rate of acid hydrolysis of methyl acetate.

It will be seen that those tetrazoles with hydrogen in position 1 (or 2) on the ring show the usual range of strengths of organic acids. Although exact measurements are not available, other tetrazoles of this type exhibit confirmatory behavior; thus, 5-phenyltetrazole can be titrated with strong bases, using phenolphthalein as the indicator (66). It is probable that all 5-monosubstituted tetrazoles are acids with constants of 10^{-7} or larger. The K_b values of the *N*-substituted methyl- and ethyl-tetrazoles, calculated from the hydrolysis constants of the hydrochlorides, indicate these compounds to be of the same order of basicity as aniline. Consistent with this or indicating an even lower degree of basicity is the observation of Bladin (6) that 2-phenyltetrazole dissolves in concentrated acids, but is reprecipitated by the addition of water.

TABLE 1

Dissociation constants of tetrazole derivatives

COMPOUND	TEMPERATURE	K_a	HYDROLYSIS CONSTANT	K_b	REFERENCES
	°C.				
Tetrazole	25	1.28×10^{-5}			(76)
5-Carbethoxytetrazole	20	4×10^{-5}			(77)
5-Aminotetrazole	25	6.8×10^{-5}			(3, 4)
5-Tetrazolecarboxamide	20	3.3×10^{-3}			(76)
2-Methyl-5-tetrazolecarboxylic acid	20	1.2×10^{-2}			(78)
1-Methyltetrazole hydrochloride			4.7×10^{-5}	2.1×10^{-10}	(74)
1-Ethyltetrazole hydrochloride			1.4×10^{-4}	7.1×10^{-11}	(74)
2-Methyltetrazole hydrochloride			2.6×10^{-4}	3.8×10^{-11}	(74)
2-Ethyltetrazole hydrochloride			4.9×10^{-4}	2.0×10^{-11}	(74)

The conductivity of a number of tetrazoles in water was determined by Oliveri-Mandalà (76), and the conductivity of tetrazole in liquid ammonia was determined by Strain (132).

No thermochemical or spectroscopic data have been reported for tetrazole or its derivatives.

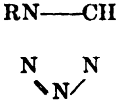
The melting or boiling points and solubilities of nearly all tetrazoles of known constitution are recorded in tables 2–7. Compounds known only as salts or those of dubious structure have been omitted. The majority of tetrazoles are crystalline solids. Some liquid tetrazoles, however, are found in each class, except for the 5-monosubstituted derivatives. It is to be noted that the three known 2-monosubstituted compounds are liquids.

The tetrazoles as a class are characterized by a considerable variation in thermal stability. Exceptional stability is found in the case of 5-guanylaminotetrazole, which does not melt at 300°C. On the other hand, most tetrazole derivatives melting above 150°C. do so with decomposition. Many tetrazoles exhibit explosive properties. Tetrazole itself explodes when heated above its melting point, and inspection of the data in tables 2–7 reveals that several tetrazoles explode when heated. Statements are occasionally found in the literature that members of this class explode when touched with a hot wire; pyridotetrazole and tetrazoloquinoline show this behavior (34). Compounds containing tetrazole rings linked to chains of nitrogen atoms, such as tetrazolyl azide or 1,6-ditetrazolylhexazdiene, are exceedingly sensitive to heat and impact.

TABLE 2

Physical properties of the tetrazoles

1-Monosubstituted tetrazoles



SUBSTITUENT	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
Hydrogen (tetrazole)	155; 156		es	es	ds	ds	
Methyl	36–37		es	es	i cold	ds	(72, 120)
Ethyl		162–164/30 mm.	es	es	es	es	(85)
Phenyl	65–66		i	es		es	(28, 39, 81)
p-Tolyl	96						(28)
p-Nitrophenyl	205 (d)†		i	s	ds	ds	(28, 39)
p-Aminophenyl	155		s hot				(39)
Hydroxy(?)	145 (d)			s	ds	i	(86, 87)

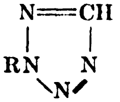
* es = easily soluble; s = soluble; ds = difficultly soluble; i = insoluble.

† d = decomposes.

TABLE 3

Physical properties of the tetrazoles

2-Monosubstituted tetrazoles



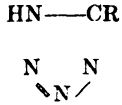
SUBSTITUENT	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
Methyl		145–147	s	s	es		(85)
Ethyl		152–155; 70–71/35 mm.					(83, 85)
Phenyl		Explodes on heating	i	es	es		(6, 145)

* es = easily soluble; s = soluble; i = insoluble.

TABLE 4

Physical properties of the tetrazoles

5-Monosubstituted tetrazoles



SUBSTITUENT OR COMPOUND	MELTING POINT*	BOILING POINT	SOLUBILITY†				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
Acetonyl	114		es	es			(107)
Phenyl	212–213 (d); 215 (d)		i cold	s	ds	ds	(66, 67, 91)
p-Tolyl	234 (d); 248		i cold	ds cold			(65, 92, 93, 123)
p-Cumenyl	189		i cold	es hot			(25)
β-Naphthyl	203 (d)			es	es		(91)
o-Chlorophenyl	177 (d)		i	es hot	ds		(123)
Anisyl	228 (d)		i cold	es	ds		(64)
3-Nitrophenyl	145		ds cold	es	s	i	(67)
4-Nitrophenyl	219		ds cold	s			(91)
3-Nitro-4-methoxyphenyl	203		ds hot		s		(64)
3-Amino-4-methoxyphenyl	223		es hot	es hot	i		(64)
α-Furyl	199 (d)		ds cold	es			(92, 94)
3,6-Di(tetrazolyl-5)-1,2,4,5-tetrazine	Explodes on heating		es	es			(26, 63)
3,6-Di(tetrazolyl-5)-dihydro-1,2,4,5-tetrazine			i	i	i	i	(26, 62, 63)
Ditetrazolyl	254–255 (d)			i	ds	i	(63, 85)
2-Hydroxybenzoyl	172			es		s	(40)
2-Hydroxy-5-chlorobenzoyl	180						(40)
2-Hydroxy-4-methoxy-5-bromobenzoyl	236 (d)						(40)
Carbethoxy	85–86		s	s			(73)
Carboxamide	234 (d)		es hot	es	i	i	(85)
N,*N*-Diethyl carboxamide	80–81						(43)
Hydrazidine	276 (d)						(63)
Cyano	99		es				(83, 85)
Chloro	73		es	es	es		(111)

The heavy metal salts of the 5-monosubstituted tetrazoles are particularly explosive. Probably diazotetrazole represents the extreme in explosive proper-

TABLE 4—*Continued*

SUBSTITUENT OR COMPOUND	MELTING POINT*	BOILING POINT	SOLUBILITY†				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
Bromo	156; 147–148		s; i	es hot; ds	es	i cold; s hot	(73, 111)
Iodo	d 190		es hot	es hot	ds		(111)
Hydroxy	254 (d)		s	s	s		(39, 111, 112)
Methoxy	159 (d)		es hot	es	ds	i	(112)
Ethoxy	98		es	es	es		(112)
Mercapto	205 (d)		es	es	es	i	(39)
Methylmercapto	151 (d)						(39)
Methyl sulfone	120		es	es	es	es	(39)
Sulfonic acid							(39)
Amino	203 (d)		1.17 at 18°C.	ds	i		(44, 111, 136)
Aldol imine	170		s	ds hot	i		(118)
Diethylacetylamino	238 (d)		ds	es hot	ds		(127)
α-Ethylcrotonylamino	240 (d)		ds hot	es hot	s		(127)
α-Bromoisovalerylamino	205 (d)		es hot	es	s		(127)
N-Tetrazolyl-5-diethylmalonic acid monoamide	188		s	es	s		(127)
Diethylmalonylbis(tetrazolyl-5 amide)	287		ds	ds hot	i		(127)
N-Methyl-*N'*-tetrazolylurea	d 265			ds			(108)
N-Phenyl-*N'*-tetrazolylurea	245 (d)		i	ds hot	i		(111)
5-Tetrazolylurethan	256 (d)		ds hot	ds hot	i		(111)
Guanylamino	Does not melt 300°C.		s	s hot	i		(111)
Benzoylamino	284		i	ds hot	i	i	(120)
Anilino	206		s hot	es hot	ds		(117, 120)
Phenylmethylamino	139		es hot	s	s		(120)
Phenylethylamino	170		es hot	s	s		(120)
Phenylbenzylamino	144		es hot	es	s		(120)
2,4-Dinitrophenylamino	174 (d)		ds hot	ds hot	i		(128)
Picrylamino	224		ds	ds	i		(128)
Phenylsulfonamido	132–134						(27)

TABLE 4—*Continued*

SUBSTITUENT OR COMPOUND	MELTING POINT*	BOILING POINT	SOLUBILITY†				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
p-Tolylsulfonamido	146–147						(27)
p-Nitrobenzenesulfonamido	185–186 (d)		0.008 at 37°C.				(97)
Hydrazino	199 (d)		ds cold	i	i	i	(137, 139, 140)
Dibromoformaldehyde 5-tetrazolylhydrazone	177 (d)		ds cold	es	ds	ds	(137)
Acetone 5-tetrazolylhydrazone	181.5		ds cold	es			(139)
Benzal 5-tetrazolylhydrazone	235		i	ds hot		i	(48, 140)
Acetophenone 5-tetrazolylhydrazone	235		i	ds			(139)
5,5′-Hydrazotetrazole	Explodes without melting		i hot				(137)
1-(5-Tetrazolyl) semicarbazide	211 (slow); 218 (rapid)		ds cold				(139)
1-(5-Tetrazolyl)-3-methyl-5-pyrazolone	215 (d)						(140)
Tetrazole-5-azo-acetoacetic acid ethyl ester	140–141		s hot		ds	i	(19)
Tetrazole-5-azo-acetoacetic acid ethyl ester phenylhydrazone	192–193 (d)			ds hot	i	i	(19)
Tetrazole(5-azo-4)(1-phenyl-3-methyl-5-pyrazolone)	201 (d)						(19)
Tetrazole(5-azo-1) naphthylamine (2)	Explodes 184		ds	ds			(136, 140)
Tetrazole-5-azo-4-*N*,*N*-dimethylaniline	Explodes 155		ds		ds		(136)
Azido	Explodes		es	ds		ds	(47, 50, 139)
1,3-Ditetrazolyl-5-triazene	Deflagrates						(46, 47)

TABLE 4—*Concluded*

SUBSTITUENT OR COMPOUND	MELTING POINT*	BOILING POINT	SOLUBILITY				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
1-Tetrazolyl-3-*p*-nitrophenyltriazene	169		i	s hot	ds		(111)
p-Sulfamylphenyldiazoaminotetrazole	175						(134)
3-Phenyl-1-tetrazolyl-5-tetrazene-1	d 139						(47)
4-Tetrazolyl-5-tetrazene-1-carboxamide	122		ds				(47)
4-Tetrazolyl-5-tetrazeneguanyl-1	d 142		ds				(47)
4-Benzal-3-guanyl-1-tetrazolyl-5-tetrazene-1	d 132						(47)
1,6-Ditetrazolyl-5-hexazdiene	Explodes 90						(47)

* d = decomposes.

† s = soluble; i = insoluble; es = easily soluble; ds = difficultly soluble. Solubility data, when given, are in grams of solute per 100 g. of solvent.

ties; aqueous solutions of it explode at 0°C. if more concentrated than about 2 per cent (136, 140).

The impression should not be gained, however, that all tetrazoles are dangerous compounds. For the most part they are probably no more dangerous than the acyl azides, and may be handled safely with the precautions customarily bestowed upon organic compounds.

III. Synthesis of Tetrazoles

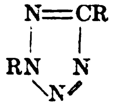
A. TETRAZOLE

The synthesis of tetrazole from hydrogen cyanide and hydrogen azide has already been mentioned. This reaction, as described by Dimroth and Fester (30), requires heating a dilute alcoholic solution of hydrazoic acid with anhydrous hydrogen cyanide in a sealed tube for 2 or 3 days at 100°C. Tetrazole is said to be formed in 80 per cent yield. There is a patent claim (96) that dilute hydrogen cyanide and hydrazoic acid may be used, but whether this pertains to

TABLE 5

Physical properties of the tetrazoles

2,5-Disubstituted tetrazoles



SUBSTITUENT OR COMPOUND		MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
2	5			Water	Alcohol	Ether	Benzene	
		°C.	°C.					
Methyl	Carboxylic acid	204–205 (d)†		s	s	ds	i	(85)
Methyl	Cyano		100–102/16 mm.	i				(85)
Ethyl	Carboxylic acid	124–125 (d)		es	ds	ds	i	(40, 83)
Ethyl	Carboxamide	125–126		ds	ds	ds	i	(83)
Ethyl	Cyano		127/45 mm.	i				(83)
Phenyl	Methyl	40	140/15 mm.			s		(32)
Phenyl	Phenyl	101.5–102		i				(31)
Phenyl	4-Hydroxyphenyl	190–191		ds cold	s	s warm	s	(145)
Phenyl	4-Aminophenyl	156		i	s	s warm	s warm	(145)
Phenyl	4-Nitrophenyl	199–200			ds	ds	s	(144)
Phenyl	Carboxylic acid	138		s	es	ds		(6, 29, 33, 145)
Phenyl	Carboxylic acid methyl ester	116		ds	es	ds		(6)
Phenyl	Carboxylic acid ethyl ester	73.5–74		ds	es	es		(6)
Phenyl	Carboxamide	167.5–168.5 (d)		ds cold	ds	ds		(6)
Phenyl	Thiocarboxamide	168–169 (d)			es			(9)
Phenyl	Carboxylic acid hydrazide	200 (d)		ds hot	s hot	i		(124)

Phenyl	Carboxylic acid azide	100 (d)		i	es	es		(124)
Phenyl	Carboxylic acid amidoxime	176–177.5 (d)		i	es warm			(8)
Phenyl	Carboxylic acid amidoxime acetate	204		i	i			(8)
Phenyl	Carboxylic acid amidoxime benzoate	205–206 (d)		i	i			(8)
Phenyl	Cyano	55.5–56		i	es	es	es	(5, 10, 146)
Phenyl	Amino	142		ds hot	es	es		(124)
Phenyl	Benzalamino	123 (d)		i	es	ds		(124)
Phenyl	Acetylamino	177 (d)		i	es	ds		(124)
Phenyl	Benzoylamino	164		i	es hot	s		(120)
Phenyl	Ethylcarbamyl	106		ds hot	es	es		(124)
Di(2-phenyl-5-tetrazolyl)urea . .		216 (d)		i	ds hot	i		(124)
5,5′-Hydrazodi(2-phenyltetrazole)		184 (d)		i	ds hot	ds		(124)
5,5′-Azodi(2-phenyltetrazole)		148		i	i	i		(124)
4-Bromophenyl	Phenyl	122			ds			(31)
2,4-Dibromophenyl	Phenyl	127			s hot			(21)
2-Aminophenyl	Phenyl	80		ds hot	s	s	s	(95)
4-Aminophenyl	Phenyl	164		i hot		i	ds cold	(95)
4-Aminophenyl	Carboxylic acid	196 (d)						(10)
2-Methyl-4-aminophenyl	Phenyl	121		ds hot	s		es	(95)
2-Chloro-4-aminophenyl	Phenyl	134		s hot	s	s	s	(95)
4-Nitrophenyl	Carboxylic acid	175 (d)						(10)

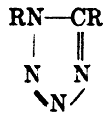
* ds = difficultly soluble; es = easily soluble; i = insoluble; s = soluble.

† d = decomposes.

TABLE 6

Physical properties of the tetrazoles

1,5-Disubstituted tetrazoles



SUBSTITUENT OR COMPOUND		MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
1	5			Water	Alcohol	Ether	Benzene	
		°C.	°C.					
Methyl	Methyl	70–71						(55)
Methyl	Phenyl	102–103	144–146/0.3 mm.	es hot	es	ds		(16)
Methyl	*p*-Tolyl	113	160/0.4 mm.					(16)
Methyl	*p*-(Diethylaminomethyl)-phenyl	109	175/0.5 mm.					(16)
Methyl	Hydroxy	122		es	s	s	es hot	(120)
Methyl	Mercapto	126		s hot	es cold	es		(131)
Bis(1-methyltetrazolyl-5) sulfide		184		s hot	s hot	i		(120)
Bis(1-methyltetrazolyl-5) disulfide		113		es hot	ds hot	i		(120)
Methyl	Amino	222		es hot	s hot	i		(113)
1,1′-Dimethyl-5,5′-hydrazotetrazole		158 (d)†		es hot	es hot	i		(113)
1,1′-Dimethyl-5,5′-azotetrazole		182 (d)		es hot	s hot	i		(113)
Dimercaptomethane bis(1-methyl-5-tetrazolyl) ether		157		es hot	s hot	i		(121)
Diphenylenedimercaptomethane bis(1-methyl-5-tetrazolyl) ether		172		i	s hot	i		(126)
Allyl	Mercapto	69		es	es	es		(131)
Butyl	Phenyl		190–193/12 mm.					(16)

tert-Butyl	Phenyl	102						(106)
n-Hexyl	Amino	162		ds cold	es			(15)
n-Hexyl	Acetylamino	106		ds cold	es			(15)
Octyl	Phenyl		205/0.5 mm.					(16)
8-Carboxyoctyl	Amino	152						(15)
8-Carbethoxyoctyl	Amino	116						(15)
Bis(5-amino-1,1′-tetrazolyl)-1,8-octane		250						(15)
Benzyl	Methyl	50						(55)
Benzyl	Amino	187						(15)
Benzyl	Acetylamino	107						(15)
Phenyl	Methyl	97.5; 98–99		ds	es	es	es	(28, 56)
Phenyl	Phenyl	145; 146						(28, 55, 104, 105)
Phenyl	*p*-Tolyl	136						(16)
Phenyl	*p*-Carboxyphenyl	267						(16)
Phenyl	*o*-Nitrophenyl	168						(16)
Phenyl	*m*-Nitrophenyl	156						(16)
Phenyl	*p*-Nitrophenyl	177–178						(16, 105)
Phenyl	2,4-Dinitrophenyl	164						(16)
Phenyl	3,5-Dinitrophenyl	208						(16)
1,1′-Diphenyl-5,5′-ditetrazolyl		212			ds hot		s	(110, 115)
Phenyl	Chloro	124		s hot	es hot	ds	es hot	(113)
Phenyl	Bromo	151		ds hot	es hot	s		(113)
Phenyl	Iodo	d 140		i	es hot	s		(120)
Phenyl	Hydroxy	187; 188		ds hot	es			(28, 38)
Phenyl	Hydroxymethyl ether	74			es	es		(126)
Phenyl	Ethoxymethyl sulfide	56		i	s hot	i		(125)
Phenyl	Mercapto	150 (d); 152		s hot	es hot	es		(38, 75, 82, 110, 120, 131)
Phenyl	Methylmercapto	80						(38, 120)
1-Phenyl-5-tetrazolylhydroxymethyl sulfide		99		i cold	es	es		(125)
1-Phenyltetrazolyl-5-methyl sulfone		84		i	es hot	s		(120)

TABLE 6—*Continued*

SUBSTITUENT OR COMPOUND		MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
1	5			Water	Alcohol	Ether	Benzene	
		°C.	°C.					
Bis(1,1′-diphenyl-5,5′-tetrazolyl) disulfide		145–148		i				(38)
Bis(1-phenyl-5-tetrazolyl)dimercaptomethane ether		136		i	s hot	s		(121)
Bis(1-phenyl-5-tetrazolyl)-α,α′-dimercaptoethane ether		93		i	es hot	s		(121)
Bis(1-phenyl-5-tetrazolyl)-α,β-dimercaptoethane ether		150		i	ds hot	i		(121)
Ethyl dimercapto acetate bis(1-phenyl-5-tetrazolyl) ether		110		i	s hot	i		(121)
Dimercaptodiphenylenemethane bis(1-phenyl-5-tetrazolyl) ether		159 (d)		i	s hot	i		(126)
Phenyl	Amino	158–159; 160		s hot	s	i		(15, 55, 82, 110)
Phenyl	Allylamino	108		i cold	es hot	s		(113)
Phenyl	Anilino	162–163			s warm	ds	s	(80, 110)
Phenyl	Acetylamino	211						(15)
Phenyl	Benzoylamino	157		i	es hot	ds		(120)
Phenyl	Hydrazino	125 (d)		es hot	es hot	i		(113)
Phenyl	Phenylhydrazino	190 (d)		i	es	ds	ds	(110, 113)
Phenyl	Benzalhydrazino	205		i	s hot	s		(113)
1,1′-Diphenyl-5,5′-hydrazotetrazole		190 (d)		i	es	i	i	(113)
1,1′-Diphenyl-5,5′-azotetrazole		228		i	i	i		(113)
1-Phenyltetrazolyl-5-azobenzene		168		i	es hot	ds	es hot	(113)
Phenyl	Azido	99		i	es hot	ds		(90, 113)
1-Phenyl-3(1-phenyltetrazolyl-5)triazene		d 130					s	(113)
o-Tolyl	Mercapto	129; 131		i				(79, 110)
Bis(1-*o*-tolyltetrazolyl-5) disulfide		102		i	s	ds		(125)
o-Tolyl	*o*-Toluidino	152						(79, 110)
m-Tolyl	*m*-Toluidino	147						(110)
p-Tolyl	Methyl	106						(28)
p-Tolyl	Phenyl	132						(16)
p-Tolyl	*p*-Tolyl	148						(16)
p-Tolyl	Mercapto	150–151; 156 (d)			s	s		(75, 125)

Bis(1-*p*-tolyltetrazolyl-5) disulfide		166–168 (d)			ds	ds	es	(75)
Bis(1-*p*-tolyltetrazolyl-5)dimercaptomethane ether		136		i	es hot	s		(121)
p-Tolyl	Amino	176; 190		ds hot	es hot	i		(15, 110)
p-Tolyl	*p*-Toluidino	207; 211			ds	ds	s hot	(79, 110)
p-Octadecylphenyl	Phenyl	80						(16)
m-Xylyl	Mercapto	141 (d)		i	es	es		(131)
Bis(1-*m*-xylyltetrazolyl-5) disulfide		114		i	es hot	ds		(125)
m-Xylyl	Amino	198		i	es hot	i	i	(113)
α-Naphthyl	Amino	194		es hot	es hot	i		(113)
1,1′-Di-*α*-naphthyl-5,5′-azotetrazole		180 (d)		i	i	i		(113)
β-Naphthyl	Mercapto	164		ds hot	es hot	s	es hot	(131)
β-Naphthyl	Amino	193		ds hot	s hot	i		(113)
1,1′-Di-*β*-naphthyl-5,5′-azotetrazole		Explodes at 204		i	i	i		(113)
o-Carboxyphenyl	Hydroxy	d 200						(79)
p-Carboxyphenyl	Hydroxy	d over 300						(75)
p-Carboxyphenyl	*p*-Carboxyphenyl	310						(16)
m-Chlorophenyl	Amino	173 (d)		i	es hot	s		(113)
p-Chlorophenyl	Amino	213 (d)		i	ds hot	i		(113)
1,1′-Di-*p*-chlorophenyl-5,5′-azotetrazole		228 (d)		i	ds hot	i		(113)
o-Methoxyphenyl	Amino	172		s hot	es hot	s		(113)
1,1′-Di-*o*-methoxyphenyl-5,5′-azotetrazole		190 (d)		i	s hot	i		(113)
p-Ethoxyphenyl	Chloro	99		s hot	es hot	s		(113)
p-Ethoxyphenyl	Amino	197		s hot	es hot	i		(113)
p-Ethoxyphenyl	*p*-Ethoxyphenylamino	197		i	ds	ds	ds	(113)
p-Ethoxyphenyl	Hydrazino	158		s hot	es hot	i		(113)
1,1′-Di-*p*-ethoxyphenyl-5,5′-hydrazotetrazole		167 (d)		i	es	i		(113)
1,1′-Di-*p*-ethoxyphenyl-5,5′-azotetrazole		223 (d)		i	ds hot	i		(113)
p-Ethoxyphenyl	Azido	72		s hot	es	es		(113)
o-Nitrophenyl	Phenyl	168						(16)
o-Nitrophenyl	*o*-Nitrophenyl	209						(16)
m-Nitrophenyl	Phenyl	133						(16)
m-Nitrophenyl	*m*-Nitrophenyl	244						(16)

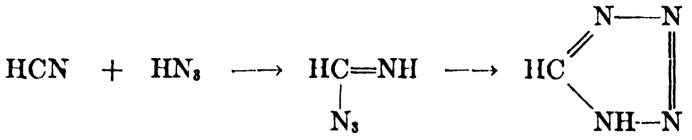
TABLE 6—*Concluded*

SUBSTITUENT OR COMPOUND		MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
1	5			Water	Alcohol	Ether	Benzene	
		°C.	°C.					
m-Nitrophenyl	*p*-Nitrophenyl	170						(16)
p-Nitrophenyl	Methyl	129						(28)
p-Nitrophenyl	Phenyl	149		i	ds			(28)
p-Nitrophenyl	*p*-Nitrophenyl	262						(16)
Hydroxy	Phenyl	121 (d); 124 (d)			es			(35, 147)
1,1′-Dihydroxy-5,5′-ditetrazolyl		Explodes 176		s hot	s			(147)
Benzoyloxy	Phenyl	127 (d)			ds hot			(35)
p-Toluenesulfonyloxy	Phenyl	91–92 (d)						(35)
β-Naphthalenesulfonyloxy	Phenyl	101 (d)			es hot			(35)
Amino	Phenyl	155		es hot	es	i		(119)
Amino	*p*-Tolyl	141		s hot	es	s		(123)
Amino	*o*-Chlorophenyl	173		ds hot	s hot	ds	ds	(123)
Amino	*p*-Nitrophenyl	154		s hot	es	s		(123)
Amino	Allylamino	94		es	es cold	ds		(114)
Amino	Anilino	210 (d)		ds hot		i	i	(114)
Phenyliminomethoxymethylamino	Phenyl	157 (d)						(122)
Phenyliminoethoxymethylamino	Phenyl	144 (d)						(122)
Isopropylideneamino	Anilino	136		i	es	i		(114)
Benzalamino	Phenyl	105		ds hot	s	s		(119, 122)
Benzalamino	Amino	210 (d)		i	s hot	i		(114)
Benzalamino	Allylamino	117		i	es hot	s		(114)
Benzalamino	Anilino	216		i	s hot	ds		(114)
Benzalamino	Benzalhydrazino	225 (d)		i	ds hot	i	ds	(114)
Anisalamino	Anisyl	147		i	ds hot	i		(122)
1,1′-Azo-5,5′-diphenyltetrazole		Explodes 141						(123)
1,1′-Azo-5,5′-di-*o*-chlorophenyltetrazole		Explodes 122						(123)

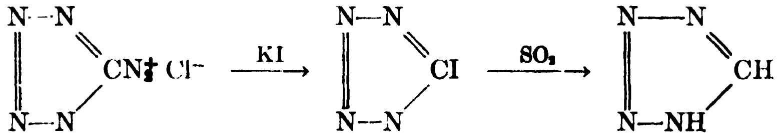
* ds = difficultly soluble; es = easily soluble; i = insoluble; s = soluble.

† d = decomposes.

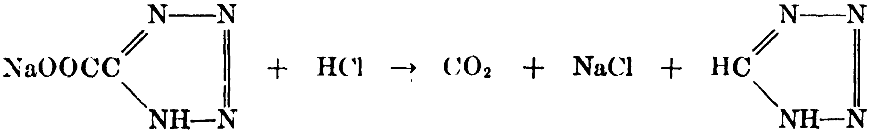
aqueous solution is not mentioned, nor are experimental details given.[1] It would be of interest to determine the mechanism and limiting conditions for this reaction. Dimroth and Fester suggested that formimidazide is formed first and subsequently rearranges to tetrazole, but no experimental evidence to support this mechanism was presented. The similarity of this direct tetrazole synthesis to the formation of 1,2,3-triazole from acetylene and hydrazoic acid (30) and to the synthesis of pyrazole from acetylene and diazomethane (88) is evident.



Tetrazole may be obtained from diazotized 5-aminotetrazole by several procedures. The sodium salt of diazotized 5-aminotetrazole may be treated with alcohol in the presence of carbon dioxide (139), or diazotetrazole may be reduced with stannous chloride and hydrochloric acid (139) or by hypophosphorous acid (111). An indirect method involves the formation of 5-iodotetrazole from diazotetrazole, and the subsequent reduction of this compound with sulfur dioxide or sodium ethylate (111).



5-Tetrazolecarboxylic acid is not stable in the free state, and tetrazole can be obtained from its salts upon acidification (73, 84, 107).



The formation of tetrazole can be achieved by the oxidation of all classes of substituted tetrazoles. Thus, 5-mercaptotetrazole, when treated with nitric

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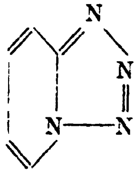
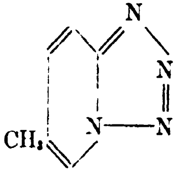
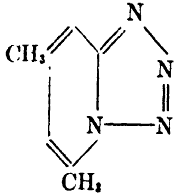
[1] The following improved directions for the preparation of tetrazole are included by the courtesy of Dr. R. M. Herbst of E. Bilhuber, Inc., Orange, New Jersey: Anhydrous hydrogen cyanide (5.4 g.) and 40 cc. of a 13.4 per cent benzene solution of hydrazoic acid are heated in a sealed tube for 96 hr. at 110°C. ± 5°. On completion of the reaction, the supernatant benzene solution is decanted from the deposit of crystals. The crystals are dissolved in warm methanol and this solution added to the benzene mother liquor. After removal of the solvents under reduced pressure on a water bath, the residue is recrystallized from 150 cc. of ethyl acetate, the tetrazole separating as small needles, melting at 156–157°C.,uncorr. Yield: 6.6 g. or 75 per cent.

TABLE 7

Physical properties of the tetrazoles

Fused-ring 1,5-disubstituted tetrazoles

COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
		°C.	°C.					
Pyridotetrazole		159		i	s	i		(16, 34)
6-Methylpyridotetrazole		152-153						(23)
5,7-Dimethylpyridotetrazole		128-129						(23)

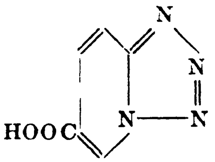
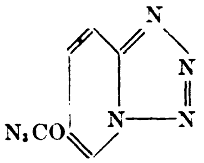
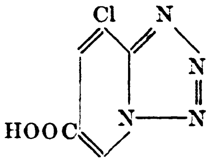
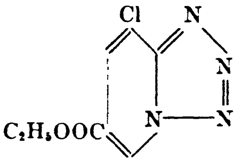
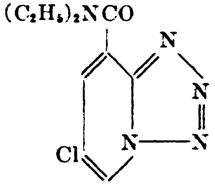
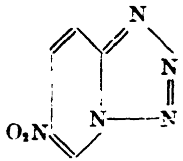
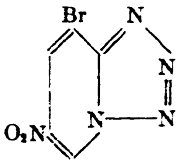
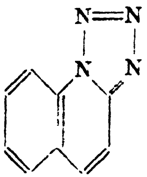
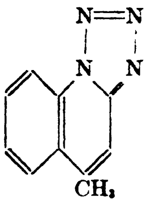
6-Carboxypyridotetrazole		Explodes over 338		s hot				(70)
6-Carboxylic acid azide pyridotetrazole		103–104		ds hot	ds cold			(70)
8-Chloropyridotetrazole-6-carboxylic acid		195–196						(41)
8-Chloro-6-carbethoxypyridotetrazole		95–96						(41)
6-Chloropyridotetrazole-8-*N*,*N*-diethylcarboxamide		113–115					s	(42)

TABLE 7—*Continued*

COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
		°C.	°C.					
Nitropyridotetrazole		142–143 (d)						(17)
·Bromo-6-nitropyridotetrazole		125						(17)
etrazolo[*a*]quinoline		157						(16, 69)
Methyltetrazolo[*a*]quinoline		207		ds hot	es			(68)

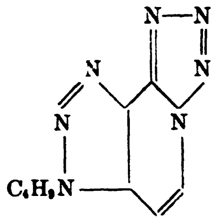
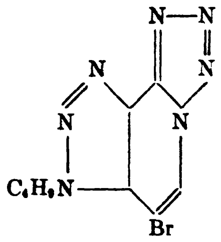
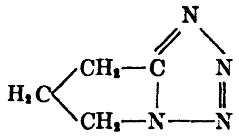
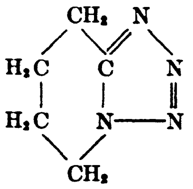
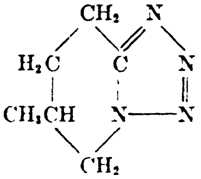
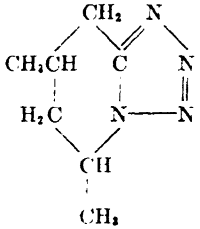
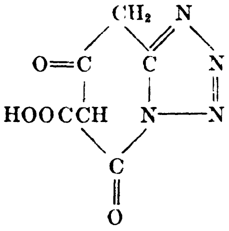
7-Butyltetrazolo[1,5-*a*]triazolo[*c*]pyridine		157–158						(17)
7-Butyl-6-bromotetrazolo[1,5-*a*]triazolo[*c*]pyridine		114						(17)
6,7-Dihydro-5-pyrrolotetrazole (trimethylenetetrazole)		110						(22)
5,6,7,8-Tetrahydropyridotetrazole (tetramethylenetetrazole)		115–116						(23)

TABLE 7—*Continued*

COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
		°C.	°C.					
6-Methyl-5,6,7,8-tetrahydropyridotetrazole		92-94						(23)
5,7-Dimethyl-5,6,7,8-tetrahydropyridotetrazole		95-97						(23)
1,3-Dioxotetramethylenetetrazole-2-carboxylic acid		d 195						(107)

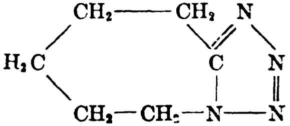
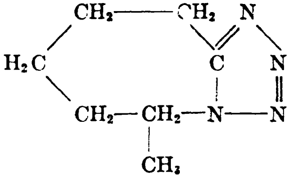
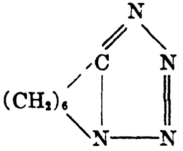
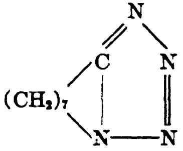
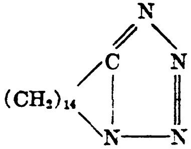
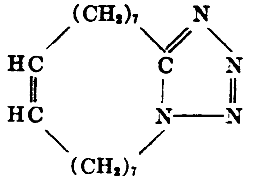
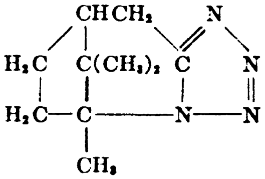
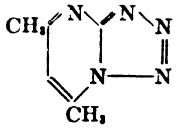
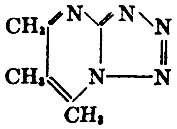
6,7,8,9-Tetrahydro-5-azepotetrazole (pentamethylenetetrazole, metrazole)		59		s				(54)
5-Methyl-6,7,8,9-tetrahydro-5-azepotetrazole		3[illegible]	185/15 mm.					(14)
5,6,7,8,9,10-Hexahydrotetrazoloazocine		66–68	135–140/ 0.1 mm.					(98)
6,7,8,9,10,11-Hexahydro-5-tetrazoloazonine			145–146/ 0.1 mm.					(98)
"Cyclotetradecamethylenetetrazole"		97–98	180–185/ 0.1 mm.		i			(98)

TABLE 7—*Continued*

COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
		°C.	°C.					
"Civetonetetrazole"		90–91	225–235/ 0.4 mm.					(99)
5,10,10-Trimethyl-6,7,8,9-tetrahydro-5,8-methano-5-azepotetrazole, "camphortetrazole"		242–243						(60, 103)
"α and β-Thujonetetrazoles"		86						(60, 103)
"β-Thujonetetrazole"		93–95						(103)
5,7-Dimethyltetrazolo[*a*]pyrimidine		151–152			es hot	i	es	(19)
5,6,7-Trimethyltetrazolo[*a*]pyrimidine		123–123.5		s hot		i	es	(19)

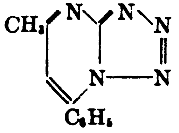
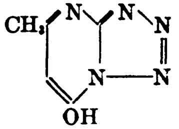
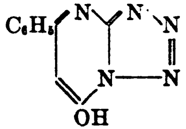
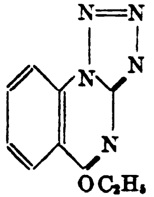
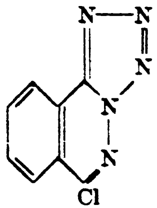
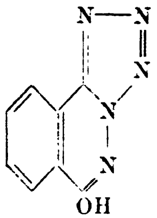
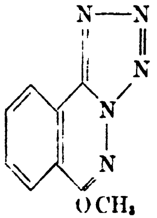
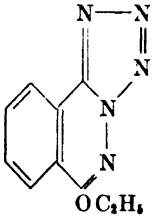
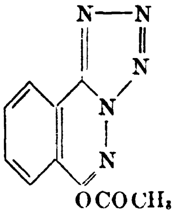
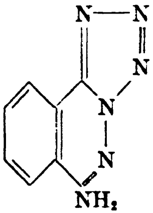
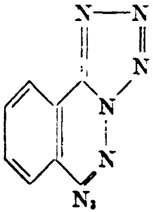
5-Phenyl-7-methyltetrazolo[*a*]pyrimidine		185				ds	ds	(19)
5-Hydroxy-7-methyltetrazolo[*a*]pyrimidine		246–247		es hot	es	ds	ds	(19)
5-Hydroxy-7-phenyltetrazolo[*a*]pyrimidine		261 (d)						(19)
Tetrazolo[*a*]-5-ethoxyquinazoline		165		i	s hot	s		(116)
Tetrazolo[*a*]-6-chlorophthalazine		195 (d)		i	ds hot	ds		(130)

TABLE 7—*Concluded*

COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
		°C.	°C.					
Tetrazolo[*a*]-6-hydroxyphthalazine		258 (d)		ds hot	ds hot	i		(130)
Tetrazolo[*a*]-6-methoxyphthalazine		211		i	s hot	ds		(130)
Tetrazolo[*a*]-6-ethoxyphthalazine		187		i	es hot	ds		(130)

Tetrazolo[*a*]-6-acetoxyphthalazine		165						(130)
Tetrazolo[*a*]-6-aminophthalazine		305		i	s hot	i	i	(130)
Tetrazolo[*a*]-6-azidophthalazine		152		i	es	ds		(130)

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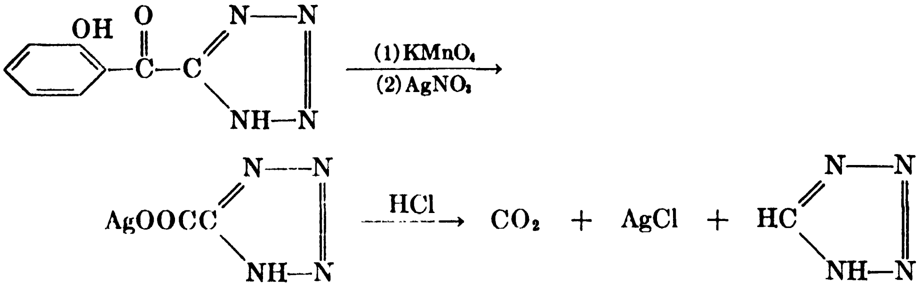
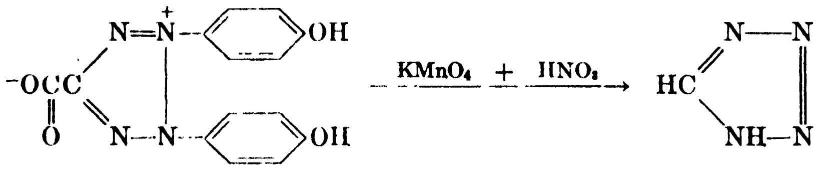
* ds = difficultly soluble; es = easily soluble; i = insoluble; s = soluble.
† d = decomposes.

acid, is converted to tetrazole (39), as is 5-(2′-hydroxybenzoyl)tetrazole when oxidized with potassium permanganate (40).



Tetrazoles substituted in the 1-position, such as 1-(*p*-aminophenyl)tetrazole (39), and fused-ring compounds such as tetrazoloquinoline (69), may be oxidized with potassium permanganate to the parent compound. In the latter example, a 97 per cent yield of tetrazole is obtained. The oxidation of 2-(*p*-aminophenyl)-5-carboxytetrazole was mentioned previously as the method used by Bladin in the first synthesis of tetrazole (10).

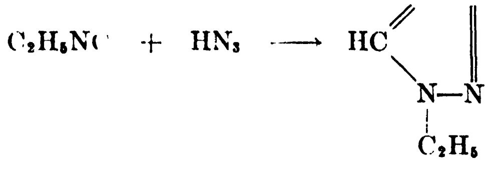
Tetrazolium salts can be oxidized similarly, as in the case of 2,3-di(*p*-hydroxyphenyl)-5-carboxytetrazolium betaine (89):



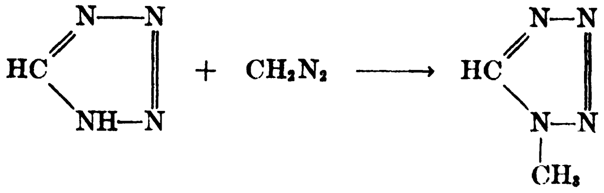
B. MONOSUBSTITUTED TETRAZOLES

1. 1-Substituted derivatives

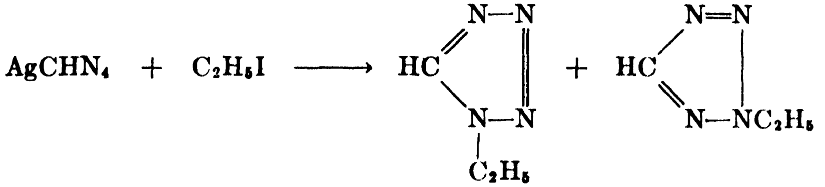
Tetrazoles substituted in the 1-position with alkyl and aryl groups may be prepared by the interaction of isocyanides and hydrazoic acid in ether solution. This synthesis of 1-substituted tetrazoles is the one most generally applicable, the methyl- (72), ethyl-, and phenyl- (81) substituted tetrazoles having been prepared by this procedure.



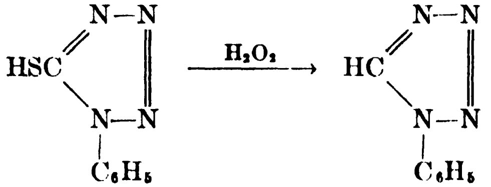
The preparation of 1-methyltetrazole has also been accomplished by the action of diazomethane on tetrazole (120), but the use of higher diazoalkanes has not been investigated.



A mixture of 1- and 2-ethyltetrazoles is produced by the action of ethyl iodide on silver tetrazole in benzene (85).



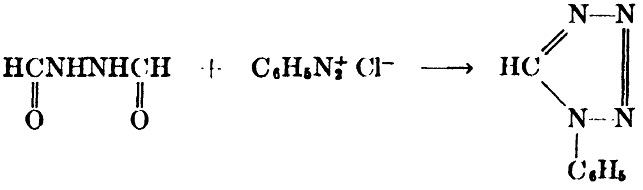
Stollé prepared 1-methyl- and 1-phenyl-tetrazoles by the action of hydrogen peroxide on the appropriate 5-mercaptotetrazole in the presence of ammonium hydroxide (120).



This reaction recalls the formation of tetrazole from 5-mercaptotetrazole by oxidation with nitric acid.

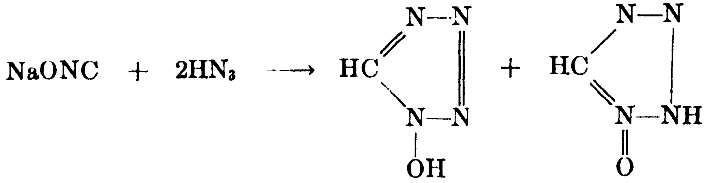
Oliveri-Mandalà observed that heating 1-phenyl-5-anilinotetrazole above its melting point (162°C.) gave rise to some 1-phenyltetrazole (80).

Certain 1-aryltetrazoles may be prepared by an interesting reaction, which involves the interaction of diazonium salts and *sym*-diformylhydrazine in the



presence of dilute sodium hydroxide. The loss of a formyl group and of a molecule of water is involved. (Further applications of this synthesis are discussed in the section on 1,5-disubstituted tetrazoles.) Dimroth and De Montmollin synthesized the phenyl, *p*-tolyl, and *p*-nitrophenyl derivatives in this way (28).

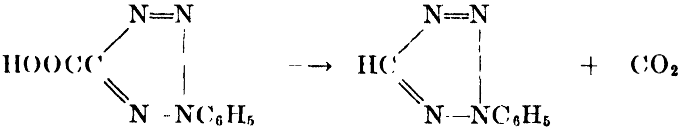
The interaction of aqueous sodium fulminate and hydrazoic acid leads to the formation of two compounds; one of these was assigned the structure of 1-hydroxytetrazole and the other 1-tetrazole oxide (86, 87). Justification for



their structures appears to be meager, being based on the behavior of the methylated derivatives obtained by interaction with diazomethane. The methyl derivative of the so-called 1-hydroxytetrazole gave results indicating the presence of a methoxyl group by the Zeisel technique, while treatment of the methyl derivative of the isomer with dilute sulfuric acid gave methylamine.

2. 2-Substituted derivatives

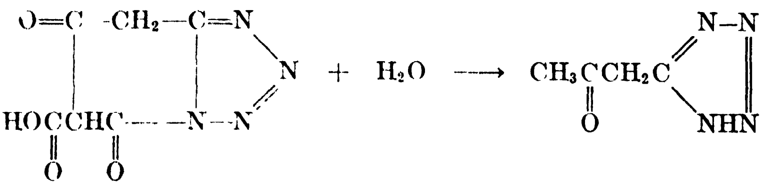
Decarboxylation of 5-carboxy-2-substituted tetrazoles has been used to obtain each of the three known 2-monosubstituted tetrazoles: namely, the methyl (85), ethyl (83), and phenyl (6, 145) derivatives.



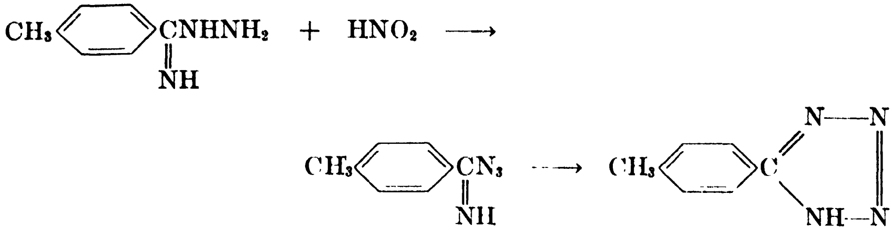
As mentioned previously, treatment of the silver salt of tetrazole with ethyl iodide yields a mixture of 1- and 2-ethyltetrazoles.

3. 5-Substituted derivatives

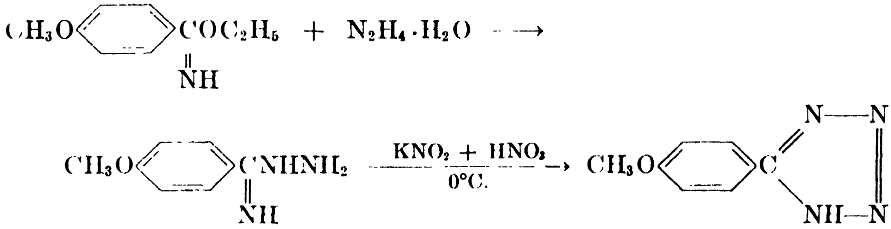
No 5-alkyltetrazoles have been reported, although there appears to be no reason why their synthesis should present undue difficulty. The preparation of 5-acetonyltetrazole has been effected by heating 1,3-dioxotetramethylenetetrazole-2-carboxylic acid with water, 2 moles of carbon dioxide being eliminated (107).



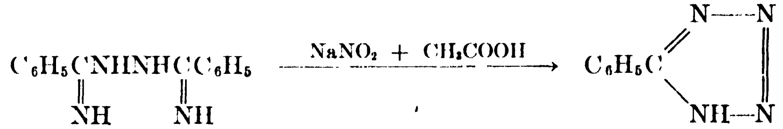
Numerous 5-aryltetrazoles have been made, the most general procedure involving the diazotization of hydrazidines. This synthesis is also useful in preparing 5-substituted tetrazoles other than aryl derivatives, and these applications will be indicated in the appropriate place. It is generally assumed that the mechanism of this synthesis involves the preliminary formation of an imide azide which subsequently rearranges to a tetrazole, either with or without the aid of a catalyst. In most cases it is impossible to isolate the intermediate imide azide. Aryltetrazoles substituted in the 5-position which have been



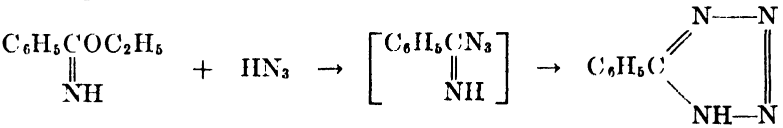
obtained by this process include phenyl (91), *p*-tolyl (92, 93), *p*-cumenyl (25), *p*-anisyl (64), *p*-nitrophenyl, and *β*-naphthyl (91). The diazotization of furoic acid hydrazidine similarly leads to 5-*α*-furyltetrazole (94). In practice, it is not always necessary to isolate the hydrazidine; these are frequently made by the interaction of imino ethers and hydrazine, and the acidified solution so obtained may be treated with a metal nitrite. This procedure was followed in the synthesis of 5-anisyltetrazole:



Another reaction leading to 5-aryltetrazoles consists in heating diaroyl imino hydrazides with sodium nitrite in acetic acid solution (91, 93). This method has been used to make 5-phenyl- and 5-*p*-tolyl-tetrazoles.

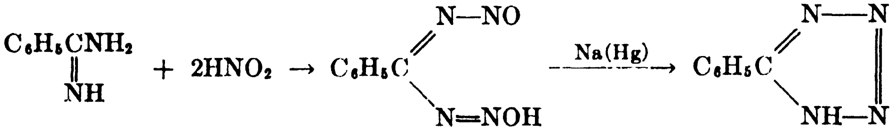


The interaction of benzimido ethyl ester and hydrazoic acid is claimed in a patent (53) to lead to 5-phenyltetrazole Presumably this reaction also proceeds through the imide azide.

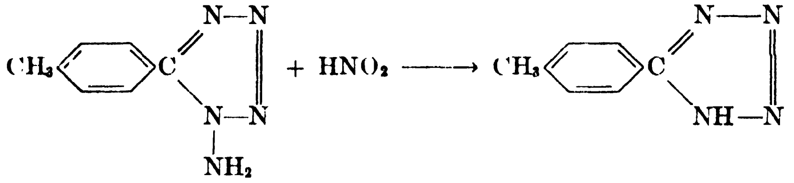


An interesting synthesis discovered by Lossen involves treating an amidine with nitrous acid to form a so-called dioxytetrazotic acid; the potassium salt of this substance is reduced in aqueous solution to a tetrazole by sodium amalgam.

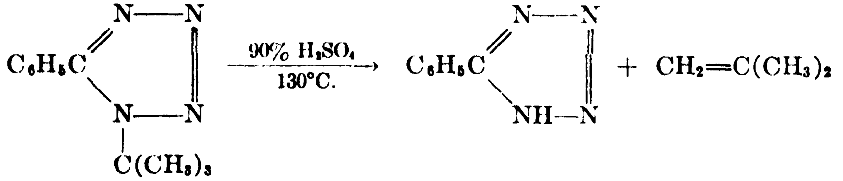
The yields obtained by this method are poor. The 5-phenyl- (66, 67) and 5-*p*-tolyl- (65) tetrazoles have been synthesized in this manner. The structure of the dioxytetrazotic acid is in doubt, but may be that indicated in the equation. This tetrazole synthesis is of particular interest, since it is the only one known which does not start with a derivative of hydrazine or hydrazoic acid.



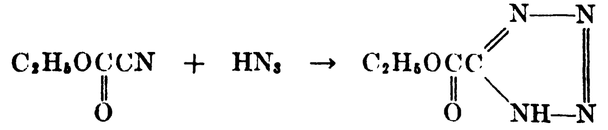
The reaction of nitrous acid and 5-aryl-1-aminotetrazoles effects replacement of the amino group with hydrogen (123). This method has been used in the preparation of 5-*p*-tolyl- and 5-*o*-chlorophenyl-tetrazoles.



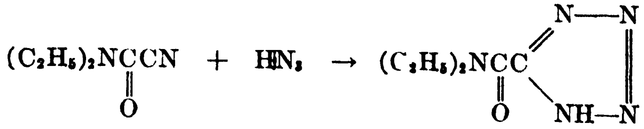
Another method of converting certain 1,5-disubstituted tetrazoles into 5-monosubstituted compounds is due to Schroeter (106), who treated 1-*tert*-butyl-5-phenyltetrazole with sulfuric acid, thereby causing elimination of 2-methylpropene.



Free 5-tetrazolecarboxylic acid does not exist, but is known in the form of its salts, ester, amides, and nitrile. The salts are obtained by alkaline hydrolysis of the nitrile or in the oxidative degradation of 5-substituted tetrazoles. In the latter case the oxidation is sometimes effected in neutral solution in the presence of silver nitrate, the insoluble silver salt of 5-tetrazolecarboxylic acid being formed (40, 107). The ethyl ester of 5-tetrazolecarboxylic acid is prepared by the combination of ethyl cyanoformate and hydrazoic acid (73):

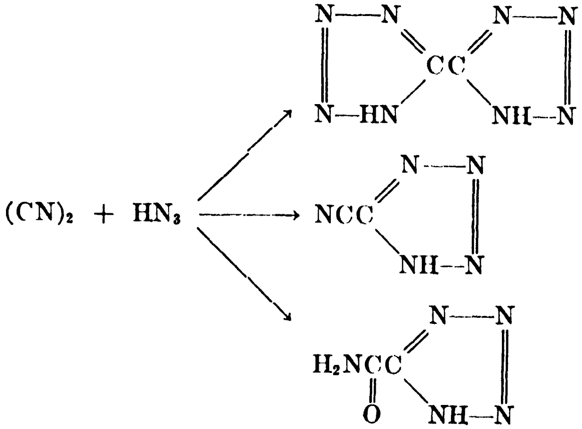


In like manner the nitrile of diethyloxamic acid and hydrazoic acid produce *N*,*N*-diethyl-5-tetrazolecarboxamide when heated in a sealed tube at 115–120°C. for 25–30 hr. (43).



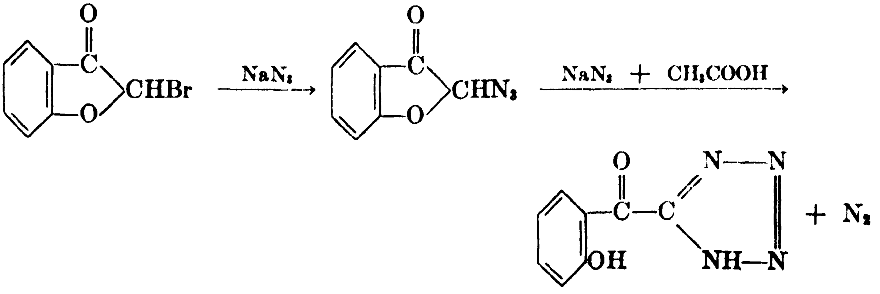
In general, the combination of hydrazoic acid with cyanides linked to a sufficiently negative group leads to 5-substituted tetrazoles. This is a reaction of considerable utility, as will be seen.

The interaction of cyanogen and concentrated aqueous hydrazoic acid in the cold results in three different compounds, depending upon the experimental conditions. Ditetrazolyl (84), 5-cyanotetrazole (62, 63, 84, 87), and 5-tetrazolecarboxamide (84) may be formed.



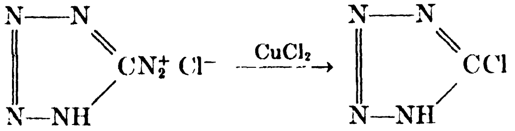
Ditetrazolyl has also been prepared from 5-tetrazolehydrazidine by diazotization (63).

Some 5-(*o*-hydroxybenzoyl)tetrazoles have been prepared from 2-azido-3-coumaranones by the action of excess sodium azide in glacial acetic acid. The azides are prepared from the bromo compounds and need not be isolated prior to conversion to the tetrazoles. It is to be noted that the formation of the tetrazole ring involves the introduction of an NH group, derived from excess hydrazoic acid, accompanied by the loss of a molecule of nitrogen. Besides the 2′-hydroxybenzoyl derivative, the 5′-bromo-2′-hydroxy-4′-methoxybenzoyl-

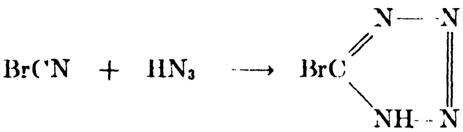


and 5′-chloro-2′-hydroxybenzoyl-tetrazoles have been synthesized by this method (40).

Stollé prepared 5-chloro-, 5-bromo-, and 5-iodo-tetrazoles from diazotized 5-aminotetrazole (111). In the case of the chloro and bromo compounds the use of cupric salts was required, while potassium iodide sufficed for the preparation of 5-iodotetrazole. These procedures in the tetrazole series thus parallel those employed in the case of diazotized aniline.

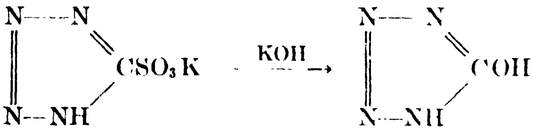


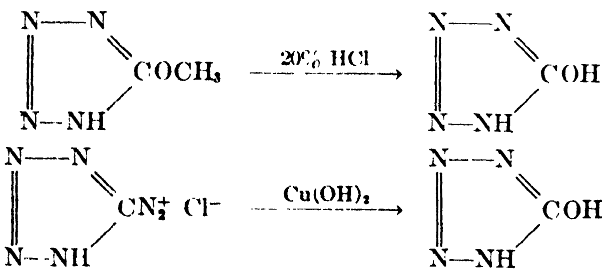
The preparation of 5-bromotetrazole has also been effected by Oliveri-Mandalà by the interaction of cyanogen bromide and hydrazoic acid in ether for several days at 50–60°C. (73).



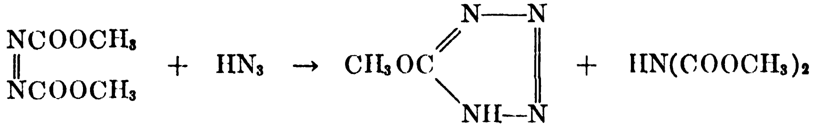
An unexplained discrepancy exists between the melting point of the 5-bromotetrazole obtained by Stollé (156°C.) and that obtained by Oliveri-Mandalà (147–148°C.).

Just as alkaline fusion of benzene- and naphthalene-sulfonic acids leads to phenols and naphthols, similarly fusion of the potassium salt of 5-tetrazolesulfonic acid with potassium hydroxide results in a small yield of 5-hydroxytetrazole (39). This compound may also be obtained by the hydrolysis of 5-methoxytetrazole with 20 per cent hydrochloric acid (112), or by treatment of diazotized 5-aminotetrazole with cupric hydroxide at 60°C. (111). Although hydrolysis of 5-chloro- or 5-bromo-tetrazole is not effected by 60 per cent sodium hydroxide, 5-iodotetrazole is converted by this reagent to 5-hydroxytetrazole (111).

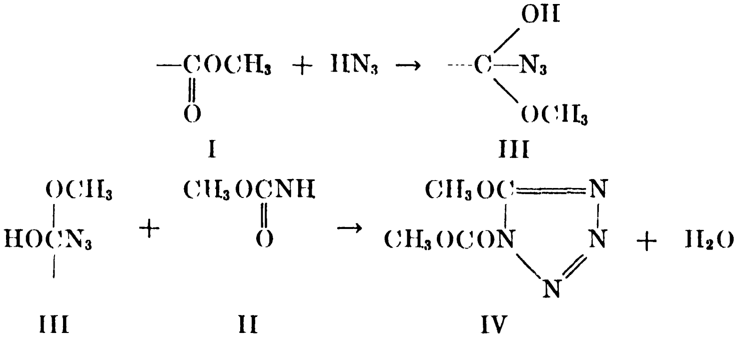




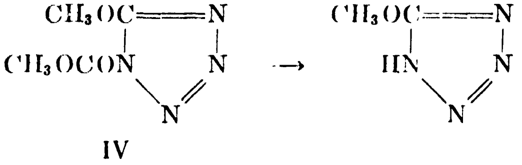
The only method by which 5-methoxytetrazole has been prepared involves a reaction discovered by Stollé and Adam (112), in which azodicarboxylic acid dimethyl ester and excess hydrazoic acid react in ether solution. Besides methoxytetrazole some iminodicarboxylic acid dimethyl ester is obtained. The mechanism suggested by Stollé for this curious reaction involves splitting



the azodicarboxylic ester under the influence of hydrazoic acid with evolution of 2 moles of nitrogen to form two residues, $—COOCH_3$ (I) and $—NHCOOCH_3$ (II). It is assumed that I combines with HN_3 to form III, which in turn unites with II to form 1-carbomethoxy-5-methoxytetrazole (IV).



Hydrolysis and decarboxylation of IV produces 5-methoxytetrazole.

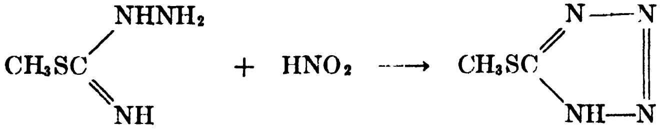


The iminodicarboxylic acid dimethyl ester arises according to this hypothesis from the combination of I and II. In the absence of more adequate proof, this mechanism must be regarded as highly speculative. Azodicarboxylic

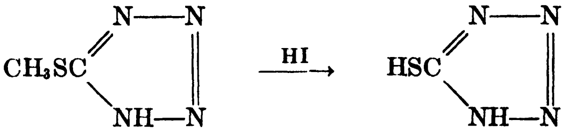
$$CH_3OCONH— + —COOCH_3 \longrightarrow HN(COOCH_3)_2$$

acid diethyl ester on treatment with hydrazoic acid yields 5-ethoxytetrazole in analogous fashion.

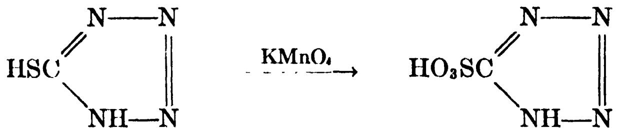
The 5-methylmercapto derivative of tetrazole was prepared by Freund and Paradies (39) from *S*-methylthiosemicarbazide by the diazotization method.



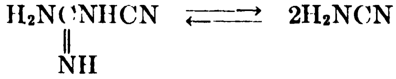
Hydrolysis of this compound with concentrated hydriodic acid in glacial acetic acid produces 5-mercaptotetrazole (39).



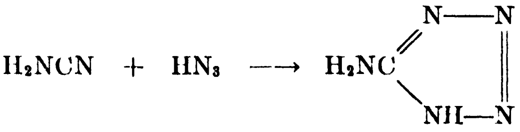
By oxidizing 5-mercaptotetrazole with 2.5 per cent potassium permanganate 5-tetrazolesulfonic acid is formed (39).

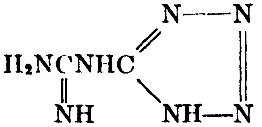


By far the most important 5-monosubstituted tetrazole is 5-aminotetrazole, since it may be used to prepare a wide variety of tetrazoles. It may be obtained by the same type of methods used in the preparation of other 5-monosubstituted derivatives. Cyanamide (44) or dicyandiamide (111, 129) may be treated with hydrazoic acid to form this compound. It is highly probable that when dicyandiamide is used, the species actually reacting is cyanamide, derived by depolymerization. This contention is supported by the fact that 5-guanylaminotetrazole, which would be formed if dicyandiamide united directly with hydrazoic acid, is stable under the conditions obtaining in this synthesis of 5-aminotetrazole (111).



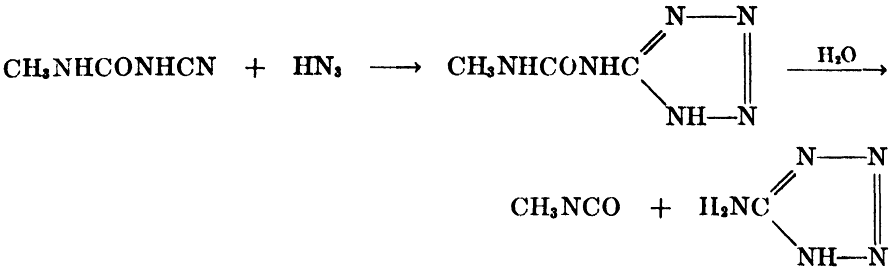
$$\underset{\substack{\| \\ NH}}{H_2NC}NHCN \rightleftharpoons 2H_2NCN$$



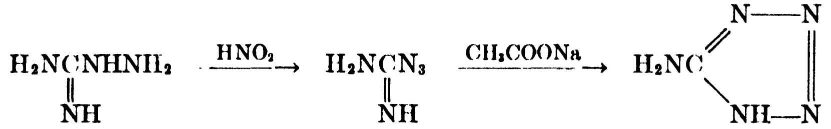


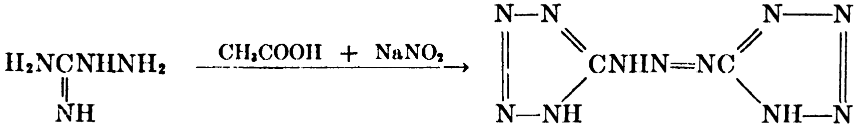
5-Guanylaminotetrazole

Interaction of *N*-methyl-*N'*-cyanourea with hydrazoic acid leads to *N*-methyl-*N'*-tetrazolylurea, which dissolves in hot water with decomposition to yield 5-aminotetrazole (108).

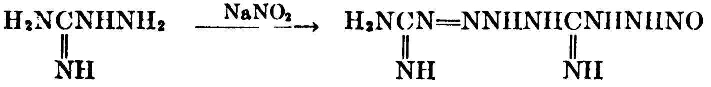


The diazotization method is applicable to the preparation of 5-aminotetrazole, and indeed was the method used by Thiele in the first synthesis of this compound. The starting material is aminoguanidine (44, 136, 138). In this case the intermediate imide azide, guanyl azide, is sufficiently stable to be isolated, and the rearrangement to 5-aminotetrazole is effected by heating with sodium acetate or carbonate. Dilute acids or merely heating with water will also effect the rearrangement. This diazotization, leading to guanyl azide, is effected by using nitric acid and sodium nitrite; aminoguanidine treated with acetic acid and sodium nitrite yields 1,3-ditetrazolyltriazene (diazoaminotetrazole), while the action of sodium nitrite alone yields 1-guanyl-4-nitrosoaminoguanyltetrazene, better known as tetracene.





Diazoaminotetrazole

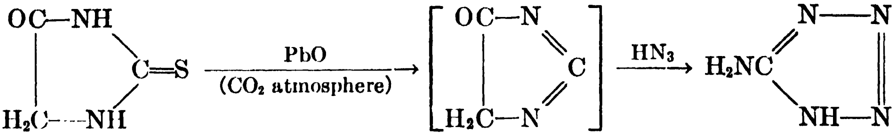


$$\underset{\displaystyle NH}{\overset{}{H_2N\underset{\|}{C}NHNH_2}} \xrightarrow{NaNO_2} \underset{\displaystyle NH}{H_2N\underset{\|}{C}}N{=}NNHNH\underset{\underset{\displaystyle NH}{\|}}{C}NHNHNO$$

Tetracene

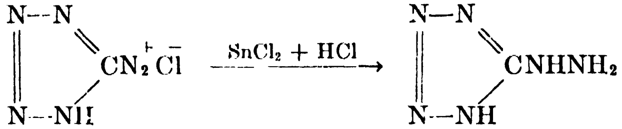
It is of interest that both of these compounds, as well as 1-guanyl-4-tetrazolyltetrazene, may be converted to 5-aminotetrazole by treatment with acids (46, 47, 49). An excellent discussion of these transformations of aminoguanidine and related compounds is to be found in the article by Lieber and Smith (61).

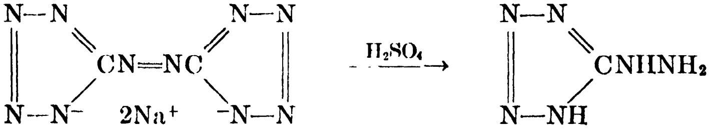
In a different category is the preparation of 5-aminotetrazole from thiohydantoin by treatment with sodium azide and lead oxide in an atmosphere of carbon dioxide (127). The mechanism of this reaction is obscure, but, by analogy with a preparative method to be discussed under 1,5-disubstituted tetrazoles, it presumably involves the formation of a cyclic carbodiimide, followed by addition of hydrazoic acid and rearrangement.

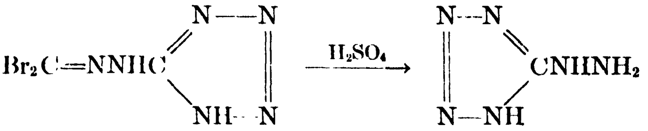


Thiohydantoin

Another 5-substituted tetrazole of importance is 5-hydrazinotetrazole, which is best obtained by reduction of tetrazolediazonium salts with stannous chloride and hydrochloric acid (139, 140). Similar treatment of tetracene (48) and 1,3-ditetrazolyltriazene (46) also leads to 5-hydrazinotetrazole. In the case of tetracene it is to be noted that ring closure occurs here, just as in the formation of 5-aminotetrazole from this material, under the influence of acid. Treatment of the sodium salt of 5-azotetrazole with acid results in the formation of 5-hydrazinotetrazole, as is also the case with dibromoformaldehyde 5-tetrazolylhydrazone (137). It should be mentioned that 5-hydrazinotetrazole is usually isolated as the insoluble benzal derivative, owing to its tendency to oxidize in air.



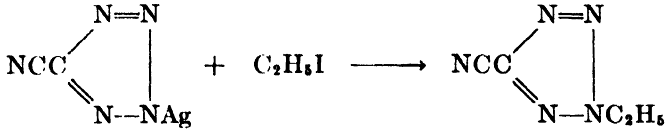




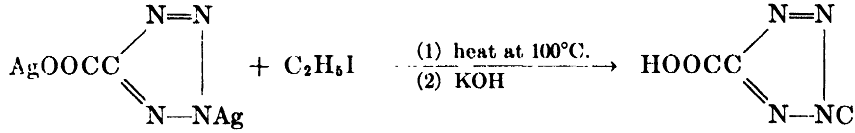
C. DISUBSTITUTED TETRAZOLES

1. 2,5 Disubstituted derivatives

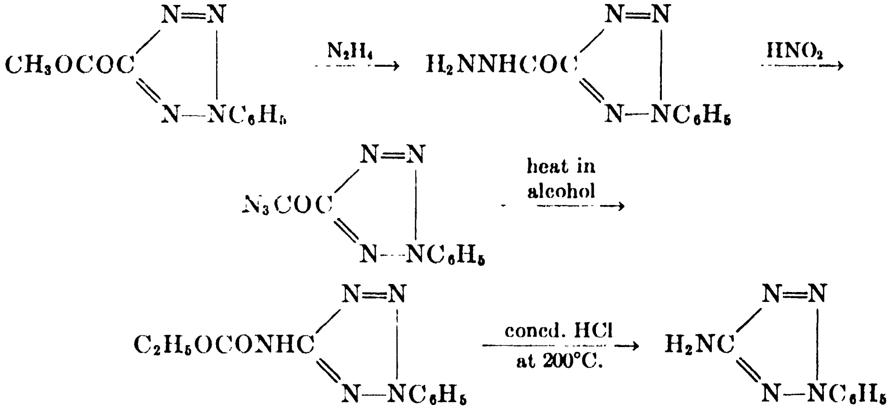
A few 2,5-disubstituted tetrazoles may be prepared from 5-monosubstituted compounds. Thus 2-methyl- or 2-ethyl-5-cyanotetrazole results from the interaction of silver cyanotetrazole with the appropriate alkyl iodide (83, 85).



Hydrolysis of the cyanide group leads to the carboxylic acids. Fries and Saftien also prepared 2-ethyl-5-tetrazolecarboxylic acid by heating silver 5-tetrazolecarboxylate and ethyl iodide at 100°C., followed by saponification with potassium hydroxide (40).

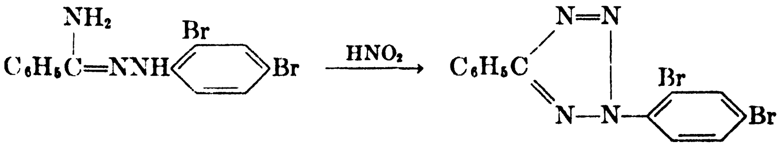


Most 2,5-disubstituted derivatives are obtained by starting with acyclic compounds. The synthesis by Bladin of 2-phenyl-5-cyanotetrazole from dicyanophenylhydrazine and nitrous acid has already been mentioned. It has not been prepared by any other method. Using this compound Bladin prepared a variety of acid derivatives by the usual methods of organic chemistry, no new syntheses of the tetrazole ring being involved. More recently Stollé and Orth (121), starting with the methyl ester of 2-phenyl-5-tetrazolecarboxylic acid prepared according to Bladin, obtained 2-phenyl-5-aminotetrazole by proceeding through the hydrazide, azide, and urethan.

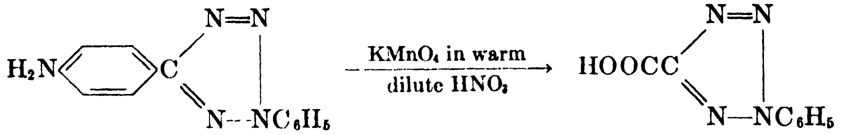


From 2-phenyl-5-aminotetrazole, or compounds intermediate in its synthesis, the corresponding urea, azo, hydrazo, acetyl, benzoyl, and benzal derivatives were prepared.

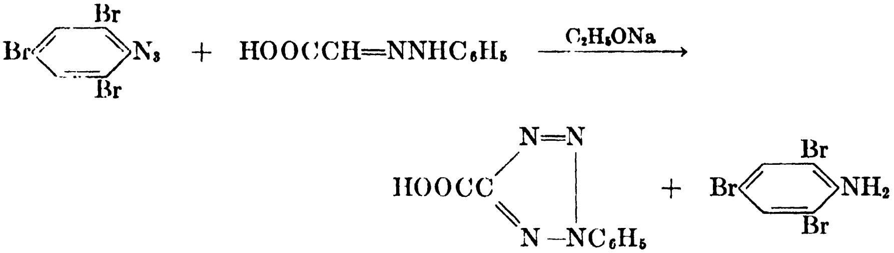
A reaction closely related to that of Bladin was used by Chattaway and Parkes (21) in the preparation of 2-(2′,4′-dibromophenyl)-5-phenyltetrazole from ω-aminobenzaldehyde 2,4-dibromophenylhydrazone and nitrous acid.



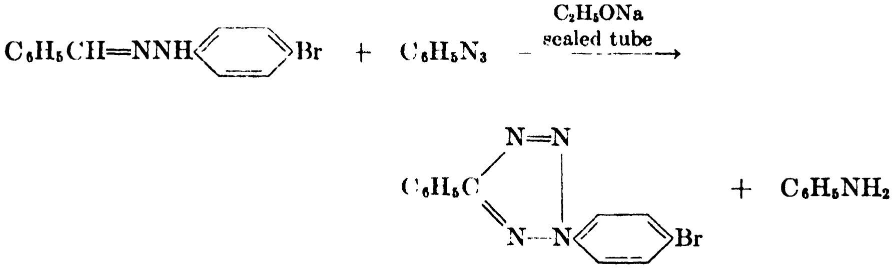
The preparation of 2-phenyl-5-tetrazolecarboxylic acid has been effected by methods other than the hydrolysis of the nitrile used by Bladin (6). Wedekind obtained it by oxidation of 2-phenyl-5-*p*-aminophenyltetrazole (145).



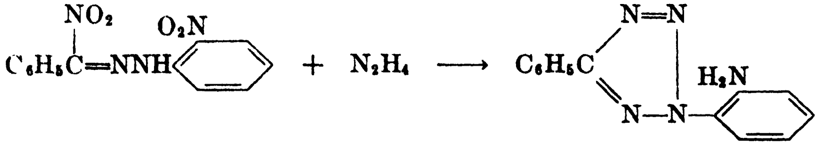
Another synthesis of this compound involves the interaction of 2,4,6-tribromoazidobenzene with the phenylhydrazone of glyoxalic acid in sodium ethylate solution (32), tribromoaniline being formed simultaneously.



This type of reaction has been extended, and other 2,5-disubstituted tetrazoles may be prepared from hydrazones by means of several reagents. Acetaldehyde phenylhydrazone and 2,4,6-tribromoazidobenzene yield 2-phenyl-5-methyltetrazole. Phenyl azide, under the more vigorous conditions of a sealed-tube reaction, is used to prepare 2,5-diphenyltetrazole, 2-*p*-bromophenyl-5-phenyltetrazole (31), and 2-(2′,4′-dibromophenyl)-5-phenyltetrazole (21) in this type reaction. The phenyl group of the phenyl azide reappears in the form of aniline.

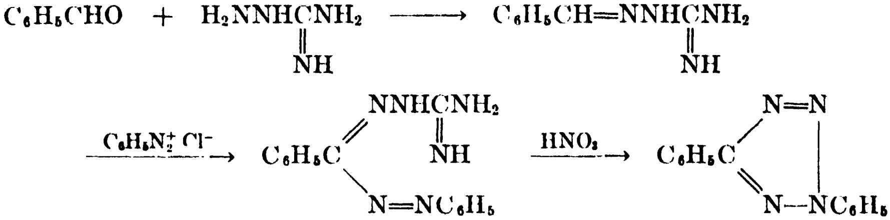


By means of the reaction of hydrazine with the *o*-nitrophenylhydrazone of phenylnitroformaldehyde, 2-*o*-aminophenyl-5-phenyltetrazole has been prepared (95).

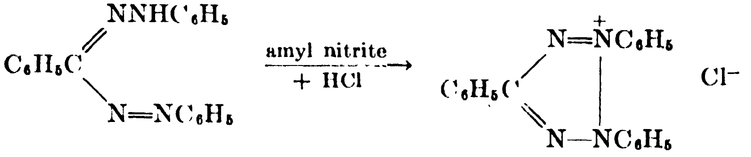


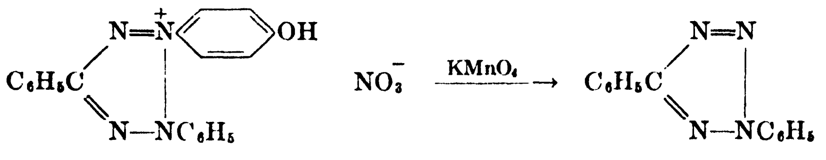
This reaction involves a displacement of the nitro group on the aldehyde moiety, and reduction of the one on the aromatic ring. The 2-*p*-aminophenyl-, *o*-methyl-*p*-aminophenyl-, and *o*-chloro-*p*-aminophenyl-5-phenyltetrazoles were obtained by this reaction.

Another synthesis of 2,5-diaryltetrazoles involves use of the coupling product of a guanylhydrazone and diazobenzene. Warming with concentrated nitric acid or with a chloroform solution of nitrogen trioxide effects ring closure. Starting with aminoguanidine and benzaldehyde, the synthesis of 2,5-diphenyltetrazole involves the following sequence:

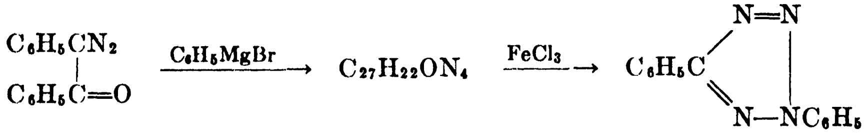


This scheme, which is due to Wedekind (143, 144), was also used to prepare 2-phenyl-5-*p*-nitrophenyltetrazole. Because of the ready availability of the starting materials, this method appears to be the best for the synthesis of 2,5-diaryltetrazoles. The structure of the intermediate "guanazyl benzene" is quite similar to that of the formazyl compounds, which may be oxidized by acidified amyl nitrite to the tetrazolium compounds. Suitably substituted tetrazolium compounds—e.g., those containing one hydroxylated phenyl group attached to nitrogen—are oxidized to 2,5-disubstituted tetrazoles. Wedekind obtained the same tetrazole derivatives in this manner that he obtained from the guanazyl derivatives (142, 144). It appears reasonable to suggest that the conversion of "guanazyl benzene" to 2,5-diphenyltetrazole proceeds through an intermediate tetrazolium compound.

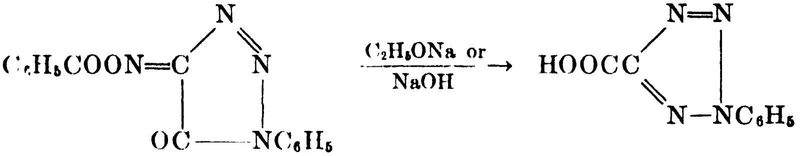




The formation of 2,5-diphenyltetrazole has also been accomplished starting with azibenzil. When this compound is condensed with phenylmagnesium bromide, an intermediate product of unknown constitution is formed, from which the tetrazole is obtained by oxidation with ferric chloride (36).

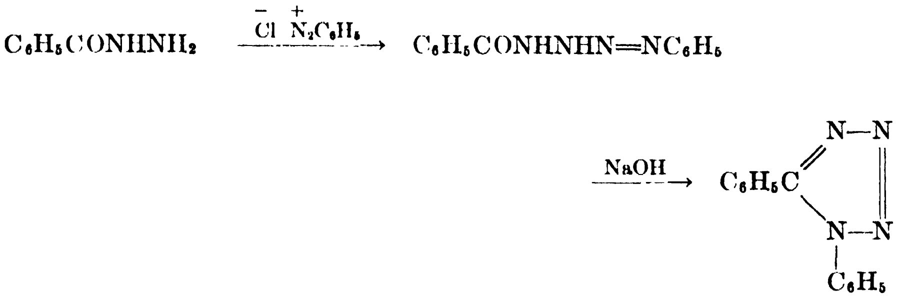


The conversion of a triazole derivative into a tetrazole has been observed in one instance. Rearrangement of the benzoyl or *m*-nitrobenzoyl derivative of 1-phenyl-5-keto-4-isonitroso-1,2,3-triazoline in alkaline solution at −10°C. gives rise to 2-phenyl-5-tetrazolecarboxylic acid (29, 33).

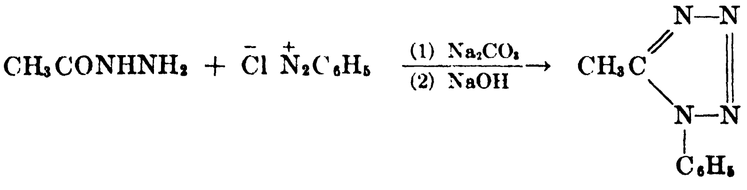


2. Simple 1,5-disubstituted derivatives

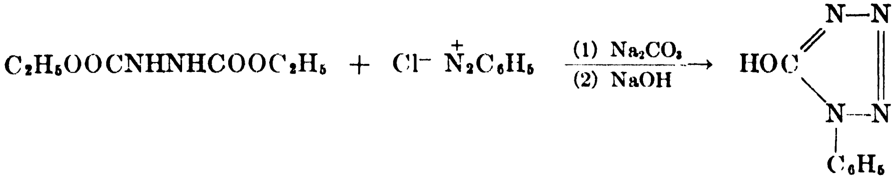
The cyclization of 1-aryl-4-acyltetrazenes to 1,5-disubstituted tetrazoles may be accomplished by use of dilute alkali. Such tetrazenes are prepared by coupling diazo compounds with acyl hydrazides. Thus 1,5-diphenyltetrazole is obtained from benzohydrazide and benzenediazonium chloride by the sequence (28):



In practice it is not necessary to isolate the intermediate tetrazene; in the case of 1-phenyl-5-methyltetrazole, sodium hydroxide is added to the reaction mixture after coupling to cyclize the intermediate. Other compounds obtained by this technique include 1-*p*-tolyl-5-methyl-, 1-*p*-nitrophenyl-5-methyl-,

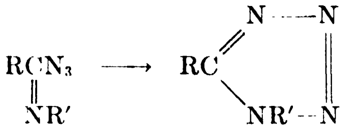


1-*p*-nitrophenyl-5-phenyl-, and 1-(phenyl-*p*-sulfonic acid)-5-methyltetrazoles. In some cases a symmetrical diacylated hydrazide is used in place of the monoacyl hydrazide, the second acyl group being eliminated during the reaction. An interesting application of this modification involves the use of diethyl hydrazinedicarboxylate and benzenediazonium chloride to prepare 1-phenyl-5-hydroxytetrazole (28). This reaction sequence is an extension of the synthesis of

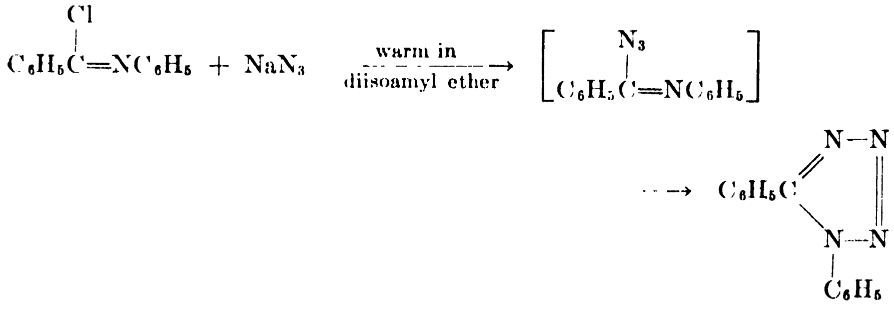


1-monosubstituted tetrazoles from diazonium compounds and symmetrical diformylhydrazine which was mentioned previously.

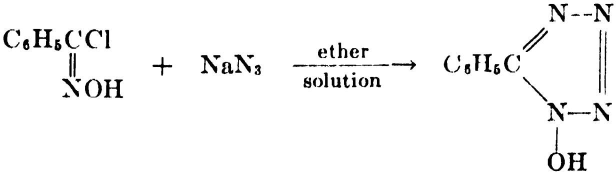
The essential step in a large number of syntheses of 1,5-disubstituted tetrazoles involves the cyclization of a substituted imide azide.



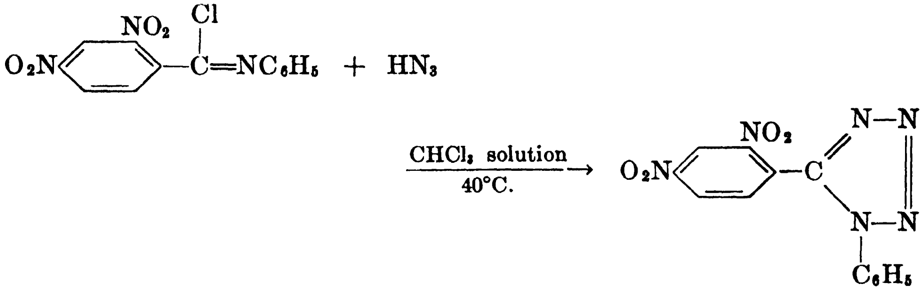
As in the case of the analogous synthesis of 5-monosubstituted tetrazoles, it is unnecessary and also frequently impossible to isolate the intermediate imide azide. The most direct method involving this type reaction starts with an imide chloride. The reaction was first applied to the preparation of simple



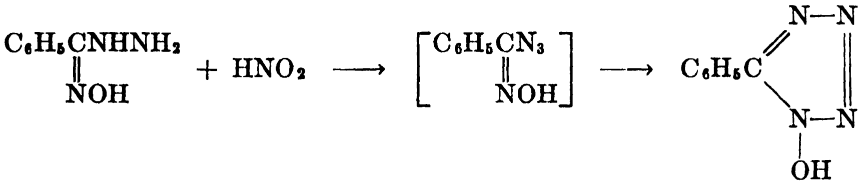
diaryl or alkyl-aryl 1,5-disubstituted tetrazoles by Schroeter (104), but was originated by Forster (35) in his synthesis of 1-hydroxy-5-phenyltetrazole from benzohydroxamic acid chloride and sodium azide.



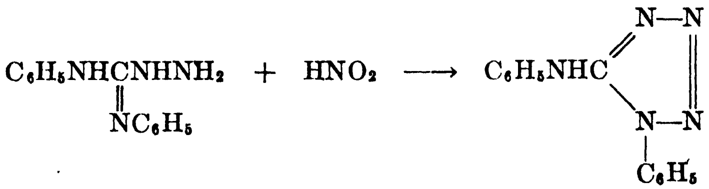
Quite recently this method has been used by von Braun and Rudolph (16) to prepare a long series of 1,5-diaryl- or alkylaryl-tetrazoles. These investigators found that many imide chlorides which do not react with sodium azide yield tetrazole derivatives if free hydrazoic acid is used in chloroform or benzene solution. Thus, nitroaromatic derivatives, which are stable to sodium azide, may be transposed by this technique.



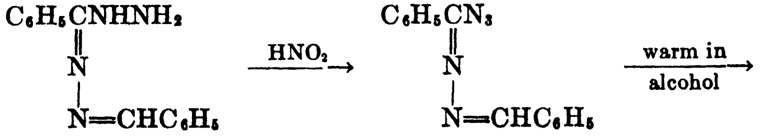
Tetrazoles of this class may also be obtained by diazotization of the appropriate hydrazide, this synthesis also proceeding through the imide azide. Wieland obtained 1-hydroxy-5-phenyltetrazole, identical with that prepared by Forster, by diazotization of benzohydrazide oxime (147). Similarly, Wieland prepared 1,1′-dihydroxy-5,5′-ditetrazolyl by the diazotization of oxalic acid dihydrazide dioxime.



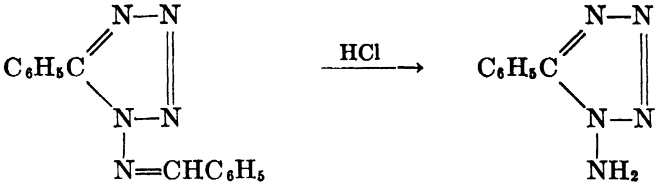
Busch and Bauer (20) obtained 1-aryl-5-arylaminotetrazoles using substituted aminoguanidines. Compounds prepared in this manner include 1-phenyl-5-anilino-, 1-*o*-tolyl-5-toluidino-, and 1-*p*-tolyl-5-*p*-toluidino-tetrazoles.



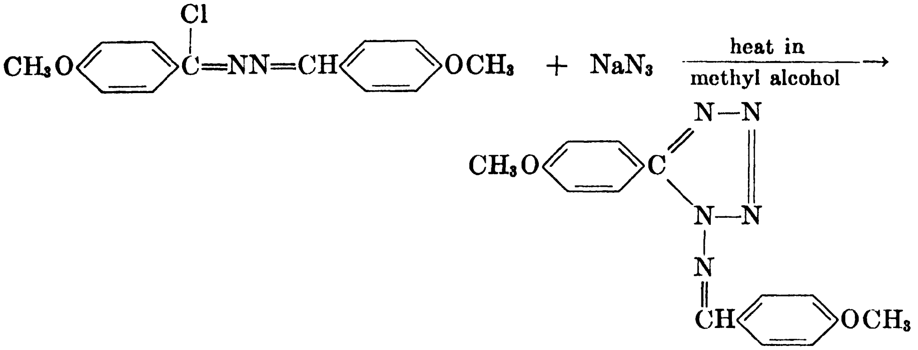
This technique enabled Stollé and Helworth (119) to obtain 1-amino-5-phenyltetrazole as indicated in the equations. In this case the intermediate



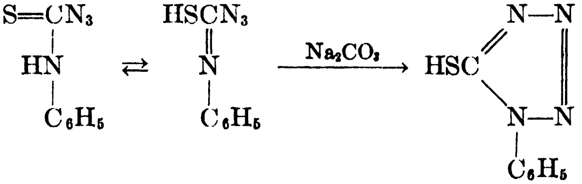
$$C_6H_5\underset{\substack{\| \\ N \\ | \\ N{=}CHC_6H_5}}{C}NHNH_2 \xrightarrow{HNO_2} C_6H_5\underset{\substack{\| \\ N \\ | \\ N{=}CHC_6H_5}}{C}N_3 \xrightarrow[\text{alcohol}]{\text{warm in}}$$

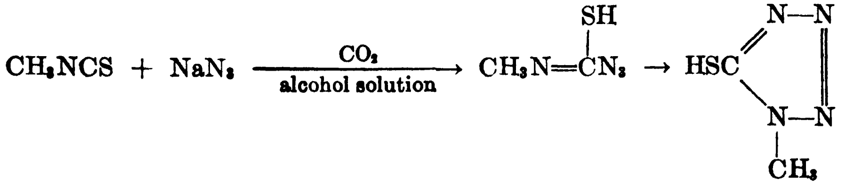


azide was stable enough to be isolated. Subsequently this azide and tetrazole were also prepared from benzal benzohydrazide chloride and sodium azide; in like manner 1-anisylideneamino-5-anisyltetrazole was prepared (122):

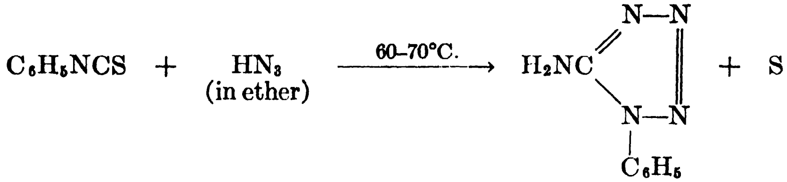


An extension of this reaction to the synthesis of 1-aryl-5-mercaptotetrazoles involves the use of compounds of the type of thiocarbanilic azide. Probably the tautomeric mercapto form is the species undergoing reaction. The rearrangement is effected by the use of alkaline reagents such as sodium carbonate or ammoniacal silver solution (38, 75). The required thiocarbamic acid azide can be obtained from isothiocyanates and hydrazoic acid under the proper conditions, and in some cases cyclization to the tetrazole may be effected merely by further heating. Thus, heating methyl isothiocyanate and sodium azide in a carbon dioxide atmosphere leads to 1-methyl-5-mercaptotetrazole (120). In like manner the 1-allyl- (131), phenyl-, *p*-tolyl- (75), *o*-tolyl- (79), *m*-xylyl, and *β*-naphthyl- (131) 5-mercaptotetrazoles have been prepared.

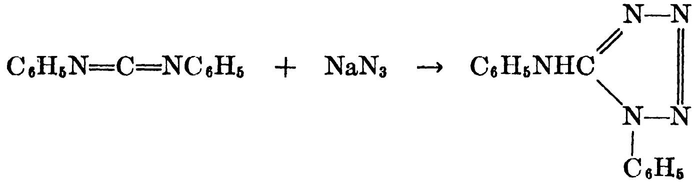


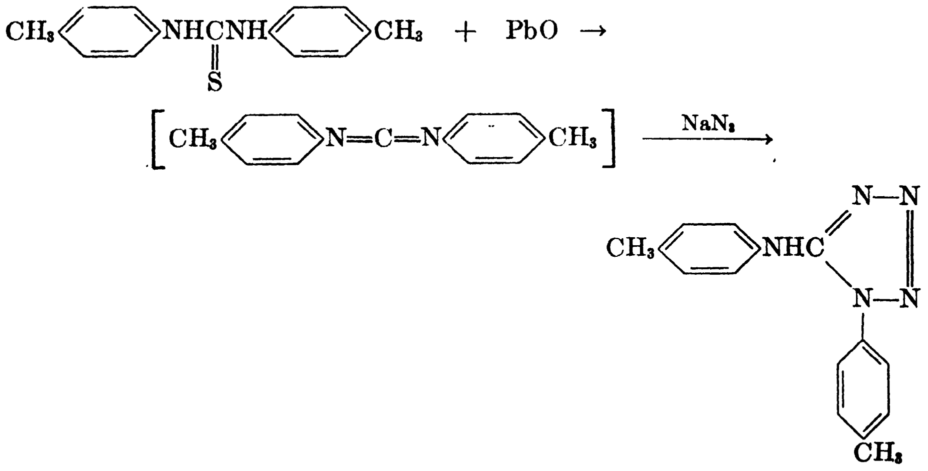


It is interesting that heating phenyl isothiocyanate with hydrazoic acid in ether under pressure results in an elimination of sulfur and formation of 1-phenyl-5-aminotetrazole (82, 110). This reaction was first performed by Oliveri-Mandalà and Noto, who believed their product to be an addition compound of hydrazoic acid and phenyl isothiocyanate. It was subsequently shown by Stollé to be sulfur free and identical with 1-phenyl-5-aminotetrazole prepared by a different method.

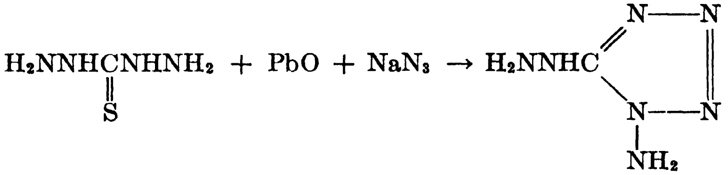


A somewhat similar reaction which has been utilized extensively by Stollé and his collaborators involves the use of carbodiimide derivatives and sodium azide or hydrazoic acid. This reaction, which was discovered independently by Oliveri-Mandalà and Stollé (80, 110), leads to 1-aryl-5-amino- or substituted amino-tetrazoles. Thus, diphenyl carbodiimide and sodium azide heated in absolute alcohol form 1-phenyl-5-anilinotetrazole. Carbodiimides are most conveniently prepared from thiourea derivatives and lead oxide; in practice it is convenient to obtain tetrazoles without isolating the intermediate by treating the thiourea derivative with lead oxide and sodium azide. It was found that interaction of di-*p*-tolylthiourea with these reagents led to 1-*p*-tolyl-5-*p*-toluidinotetrazole, identical with that obtained from di-*p*-tolylcarbodiimide. Mono-



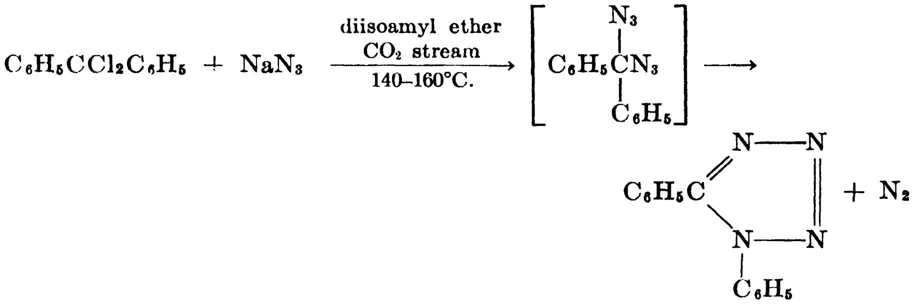


substituted thioureas may also be used; monophenylthiourea in this reaction is converted to 1-phenyl-5-aminotetrazole. This procedure may be used to prepare 1,5-diaminotetrazole by starting with thiosemicarbazide, and 1-amino-5-hydrazinotetrazole by starting with thiocarbohydrazide, both being isolated as the hydrochlorides (114). For the preparation of 1,5-disubstituted tetrazoles linked to nitrogen in the 5-position this method is probably the most convenient.

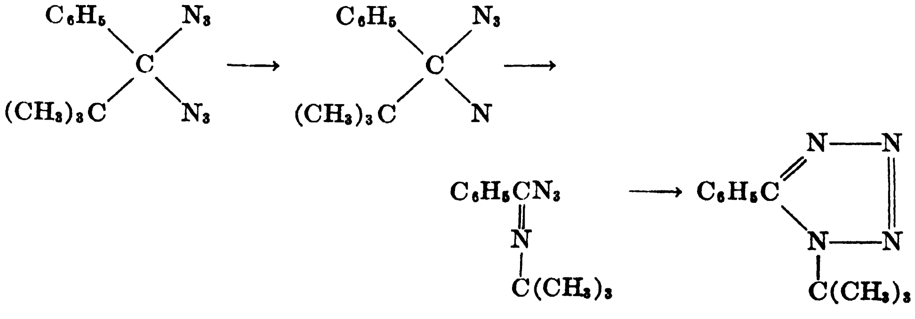


The foregoing synthetic methods have involved cyclizations without migration of alkyl or aryl radicals. Several syntheses are known in which a carbon-to-carbon link is broken and a carbon-to-nitrogen bond is established. All of these involve the use of 2 moles of inorganic azide or hydrazoic acid per mole of substrate.

The first method involves the rearrangement of the product derived from the dichloro derivatives of ketones and sodium or silver azide. Presumably the intermediate is the diazide. This method was used to obtain 1,5-diphenyl-, 1-phenyl-5-p-nitrophenyl- (104, 105), and 1-*tert*-butyl-5-phenyl-tetrazoles (106).

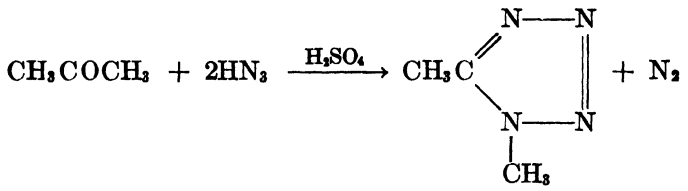


It is of interest that in these cases phenyl migrates in preference to p-nitrophenyl, and *tert*-butyl in preference to phenyl. Schroeter considers this synthesis to involve the intermediate formation of monovalent nitrogen, followed by rearrangement to the imide azide, analogous to one view of the Curtius and Beckmann rearrangements.



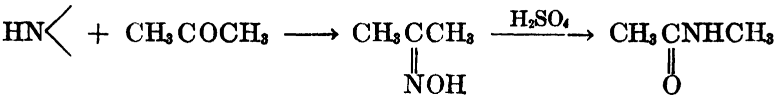
Another procedure for the synthesis of 1,5-disubstituted tetrazoles involving a rearrangement of this type is the reaction of hydrazoic acid and ketones in the presence of sulfuric acid, discovered by Schmidt (101). When 1 mole of hydrazoic acid is used per mole of ketone, *N*-substituted amides are produced; if 2 moles of hydrazoic acid are used, a 1,5-disubstituted tetrazole is formed. According to Schmidt, no tetrazole is obtained if hydrazoic acid is added to the amide under the conditions of the reaction; hence the formation of the tetrazole must involve addition to an intermediate of some sort. The mechanism offered by Schmidt to explain this and other reactions of hydrazoic acid in the presence of acid catalysts assumes the formation of the imide or imine radical, which subsequently reacts with the substrate.

$$CH_3COCH_3 + HN_3 \xrightarrow{H_2SO_4} CH_3CONHCH_3 + N_2$$

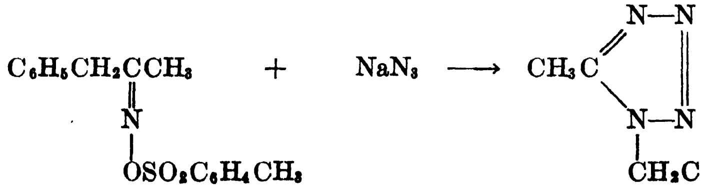


$$HN_3 \longrightarrow N_2 + HN\langle$$

Further discussion of this decomposition of hydrazoic acid is given by Audrieth (1). Interaction with ketones leads to oximes which, under the influence of the acid, undergo the Beckmann rearrangement to yield the substituted amide. While oximes do not react with hydrazoic acid to yield tetrazoles, oxime esters such as the sulfonic, benzenesulfonic, or phosphoric do undergo such reaction. Thus the *p*-toluenesulfonic ester of benzyl methyl ketoxime yields 1-benzyl-5-methyltetrazole (12). It appears reasonable to suppose that the formation of a tetrazole from a ketone involves the intermediate formation of the precursor of the oxime, possibly the oxime sulfonic ester, which further reacts with hydrazoic acid to complete the ring. There is some doubt whether the imide radical is the active entity in the initial reaction (109); since the reaction occurs in the presence

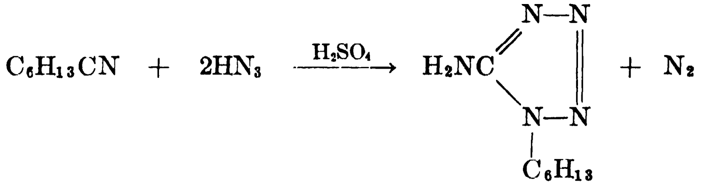


$$HN\langle + CH_3COCH_3 \longrightarrow \underset{\displaystyle NOH}{CH_3\overset{\|}{C}CH_3} \xrightarrow{H_2SO_4} \underset{\displaystyle O}{CH_3\overset{\|}{C}NHCH_3}$$

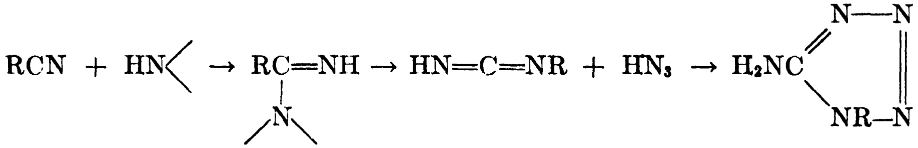


of sulfuric acid or other acid catalysts, it may be that NH_2^+ or $H_2N_3^+$ is involved. The Schmidt synthesis of tetrazoles will be considered further in connection with the fused-ring tetrazoles.

Another synthesis involving fission of a carbon-to-carbon link in the presence of sulfuric acid consists in the interaction of nitriles and hydrazoic acid. Although compounds containing a negative group joined to the cyanide radical react with hydrazoic acid to yield 5-monosubstituted tetrazoles, alkyl and aryl cyanides undergo a different reaction with this reagent. Enanthonitrile is converted to 1-hexyl-5-aminotetrazole by excess hydrazoic acid under the influence of concentrated sulfuric acid (15). In addition the 1-phenyl-, *p*-tolyl-,



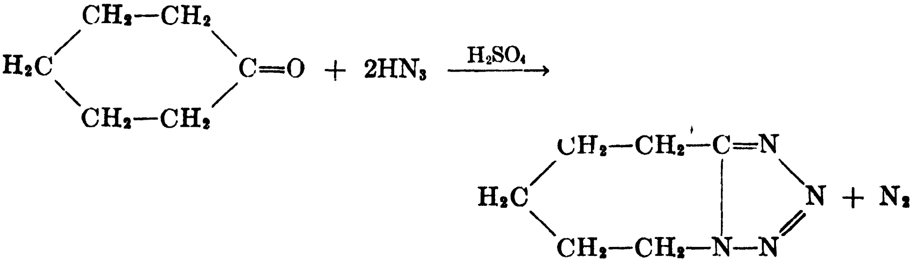
and benzyl-5-aminotetrazoles, as well as the bisaminotetrazole from sebaconitrile, have been prepared in this manner. The mechanism proposed by von Braun and Keller for this reaction involves the formation of a carbodiimide derivative by the agency of the imide radical derived from hydrazoic acid, followed by the addition of another molecule of hydrazoic acid. It is evident



that a considerable similarity exists between this reaction and that of Schmidt; both involve the insertion of a nitrogen between two carbon atoms, one of which carries a negative group and the other of which is in an alkyl or aryl group.

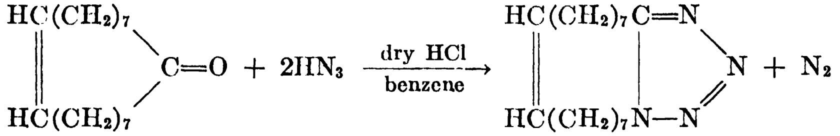
3. *Fused-ring 1,5-disubstituted tetrazoles*

The Schmidt reaction may be applied to cyclic as well as acyclic ketones, fused ring tetrazoles being formed in this instance. Metrazole, also known as cardiazole and 1,5-pentamethylenetetrazole, is obtained from cyclohexanone and a benzene solution of hydrazoic acid in the presence of an acid catalyst (101). This reaction forms the subject of a considerable number of patents



(12, 57, 58, 59, 102) and several variants in the procedure are employed. As with the simple 1,5-disubstituted tetrazoles, the interaction of ketoxime esters, or the necessary reactants for their formation, and azides may be used to obtain fused-ring tetrazoles (13, 55). Thus, cyclohexanone oxime, phosphorus oxychloride, piperidine, and sodium azide are claimed in one patent (12) to react producing metrazole. In another instance, the *p*-toluenesulfonic ester of cyclohexanone oxime is treated with hydrazine, followed by diazotization to yield metrazole (54). Since hydrazoic acid is obtained by the action of nitrous acid on hydrazine, this reaction is nearly equivalent to that of Schmidt. A further extension of this procedure is the use of azidosulfonic acid in the reaction with ketoximes (24).

Ruzicka and coworkers have applied the Schmidt reaction to higher cyclic ketones, and have prepared the expected tetrazoles (98, 99). These investigators converted civetone into a tetrazole fused to an eighteen-membered ring.

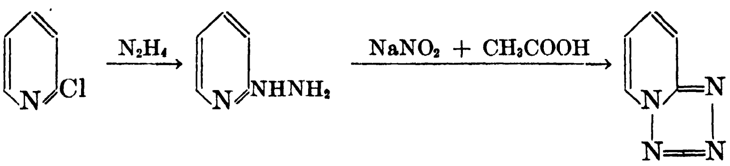


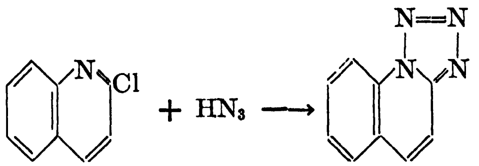
In addition the corresponding tetrazoles from cycloheptanone, cyclooöctanone, and cyclopentadecanone were synthesized. Both sulfuric acid and dry hydrogen chloride were used as condensing agents. In the course of this work Ruzicka checked the patent claims of Schmidt and others concerning this reaction and found them to be valid.

During the preparation of methyl-ϵ-leucine lactam from methylcyclohexanone and hydrazoic acid, von Braun and Heymons (14) obtained a small amount of a methylmetrazole.

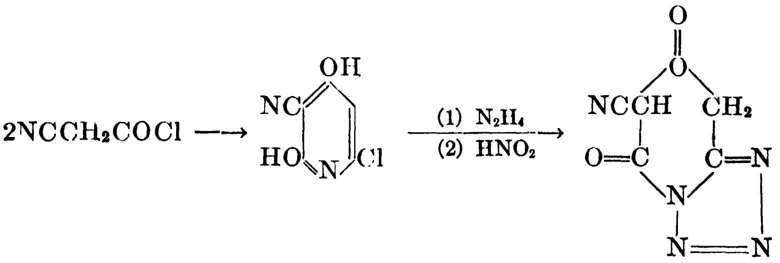
Camphor and thujone have also been employed in this reaction, yielding the corresponding tetrazoles (60, 103).

The synthesis of 1,5-disubstituted tetrazoles through the imide azide is as important in the fused-ring series as with the simple derivatives. Both the interaction of a cyclic imide chloride with hydrazine, followed by diazotization, as well as the direct action of hydrazoic acid or sodium azide on the imide chloride have been used. Pyridotetrazole was first prepared by Fargher and Furness from 2-hydrazinopyridine, which had been obtained from the chloride (34). It is to be noted that 2-chloropyridine may be considered to be an imide chloride. The work of von Braun and Rudolph (16) also included the synthesis of this compound, it being formed easily from 2-chloropyridine and hydrazoic acid. Tetrazolo[*a*]quinoline was similarly prepared. Sodium azide could not be used in these syntheses.

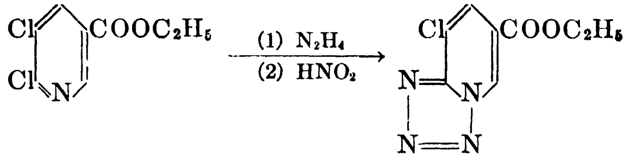




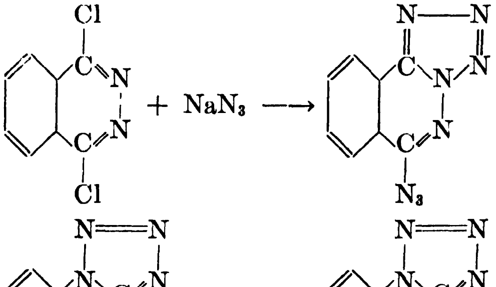
Schroeter and Finck (107), in their study of the spontaneous polymerization of cyanoacetyl chloride, prepared several tetrazole derivatives. This substance undergoes self-condensation with loss of a molecule of hydrogen chloride to form 6-chloronorricinine. Treatment of the latter with hydrazine, followed by diazotization, leads to a tetrazole, from which other derivatives were prepared.

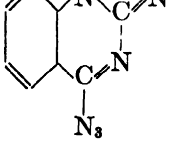


Other 2-chloropyridine derivatives were used by Graf and coworkers to obtain tetrazoles of this series (41, 42). Thus ethyl 2,3-dichloronicotinate was converted to a tetrazole by the same series of reactions:

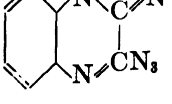


Stollé attempted to prepare bis fused-ring tetrazoles from various diimide





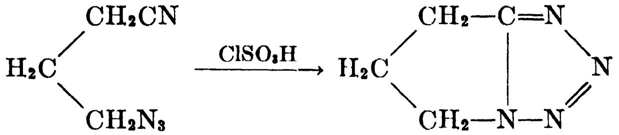
Tetrazolo[*a*]-5-azidoquinazoline



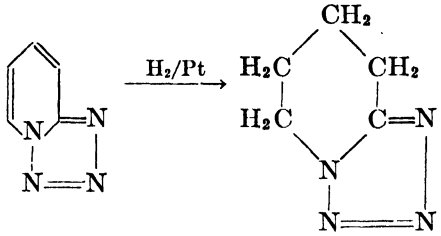
Tetrazolo[*a*]-4-azidoquinoxaline

chlorides, but was able to effect ring closure in but one position. When dichlorophthalazine was treated with sodium azide in absolute alcohol tetrazolo-[*a*]-6-azidophthalazine was formed (130). In like manner, only one tetrazole ring could be formed in the compounds derived from dichloroquinazoline or dichloroquinoxaline. The azide group in these compounds was easily replaced by hydroxyl or alkoxyl, or could be reduced to amino (115, 116).

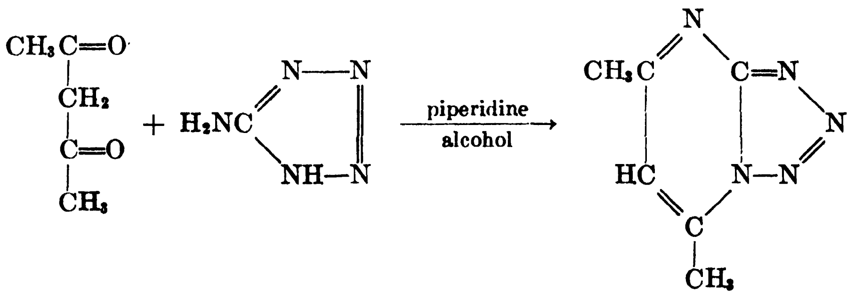
An interesting internal condensation leading to a fused-ring tetrazole is described in a patent (22): γ-azidobutyronitrile when treated with chlorosulfonic acid yields 6,7-dihydro-5-pyrrolotetrazole, otherwise known as trimethylenetetrazole. Syntheses of tetramethylenetetrazole, dimethyltetramethylenetetrazole, and the ethyl ester of tetramethylenetetrazolecarboxylic acid also are claimed to be feasible by this procedure.



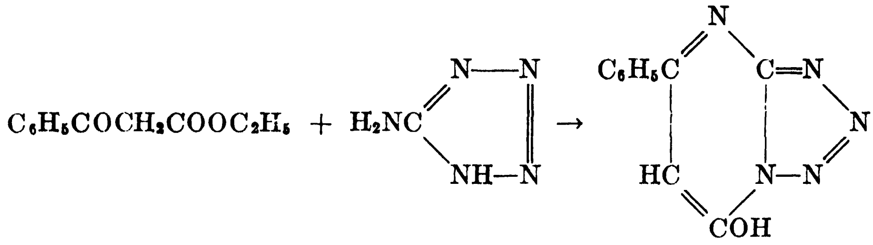
Catalytic reduction of pyridotetrazole and its alkyl derivatives is claimed in another patent to lead to tetramethylenetetrazole and derivatives (23). It should be mentioned in this connection that Roblin and coworkers (97) were unable to reduce 5-*p*-nitrobenzenesulfonamidotetrazole without splitting the tetrazole ring, although a variety of methods, including hydrogenation in the presence of palladium, were employed.



The only syntheses of fused-ring tetrazoles which have been effected starting with a monocyclic tetrazole are those of Bülow (19). This investigator condensed 5-aminotetrazole with β-diketones such as acetylacetone in alcoholic solution in the presence of piperidine to form tetrazolo[*a*]pyrimidines. Di-



methyl-, trimethyl-, and phenylmethyl-tetrazolo[*a*]pyrimidines were obtained in this fashion. Bülow also condensed β-ketonic esters with 5-aminotetrazole in glacial acetic acid solution to form hydroxytetrazolo[*a*]pyrimidines. Acetoacetic ester led to the 7-methyl derivative and benzoylacetic ester to the 7-phenyl compound.



IV. Reactions

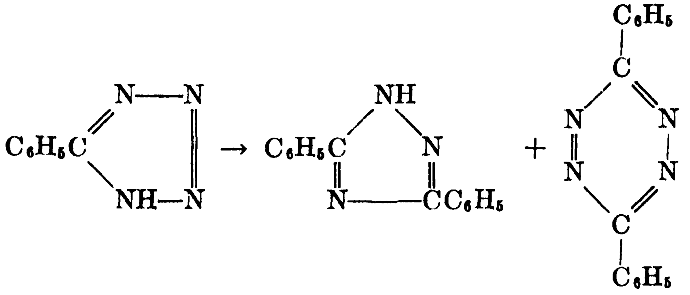
In the foregoing discussion numerous reactions of substituted tetrazoles have been recorded. It is apparent that the several organic radicals linked to the tetrazole ring can undergo the customary transformations. It is also evident that the tetrazole ring exhibits a chemical stability wholly comparable to other aromatic cycles. The material in this section, therefore, will not detail the usual organic reactions, but will indicate conditions under which the tetrazole ring is stable and by which it is broken, and the products of decomposition when ruptured.

The thermal decomposition in aqueous solution of one of the least stable tetrazoles, diazotetrazole, was studied by Thiele and Marais (139). These investigators found that 94.9 per cent of the compound decomposed to form nitrogen and cyanogen according to the equation:

$$2CN_6 \rightarrow (CN)_2 + 5N_2$$

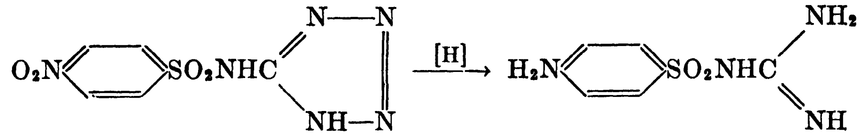
A small amount of a solid substance thought to be oxytetrazole was also formed.

The simultaneous formation of a triazole and a tetrazine occurs when 5-phenyltetrazole is heated above its melting point (91). This reaction may be considered

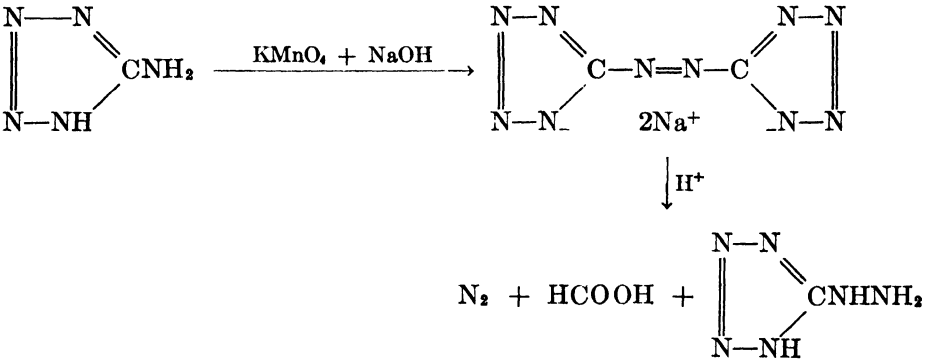


to be a type of dismutation. Similarly the extended heating of 5-*p*-anisyltetrazole at 218°C. leads to the formation of 3,5-bis(*p*-anisyl)-1,2,4-triazole (64). No other studies of the purely thermal decomposition of tetrazoles are recorded.

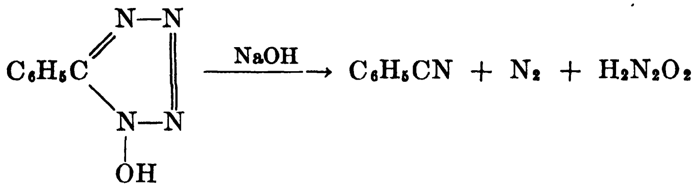
Mention has already been made of the disruption of the tetrazole ring in 5-*p*-nitrobenzenesulfonamidotetrazole during attempted reduction of the nitro group (97). Sulfanilylguanidine was formed even with such a mild reducing agent as iron and acetic acid in alcohol. On the other hand, the reported catalytic reduction of pyridotetrazole (23) reduced only the pyridine ring. The difference may lie in the greater negativity of the *p*-nitrobenzenesulfonamido group compared to that of the fused pyridine ring. Reductions of various nitrosubstituted phenyltetrazoles, however, have been carried out without splitting the heterocyclic ring. Thus, stannous chloride converts 1-(*p*-nitrophenyl)tetrazole (39) and 5-(*o*-nitro-*p*-anisyl)tetrazole (64) to the corresponding amino derivatives without ring fission.



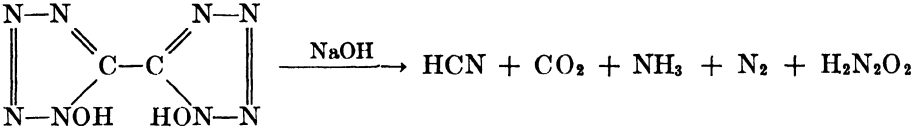
That the tetrazole ring is stable toward strenuous oxidizing agents is indicated by the various conditions under which the parent compound is formed from substituted derivatives. These were mentioned in the discussion of the synthesis of tetrazole. In the case of 5-aminotetrazole, however, treatment with weakly alkaline permanganate results in the formation of hydrogen cyanide and carbon dioxide (136). Strongly alkaline permanganate converts 5-aminotetrazole to the salt of 5-azotetrazole. When this salt is neutralized, nitrogen is liberated and formic acid and tetrazolylhydrazine are formed. It is evident that the decomposition of azotetrazole does not proceed by the same mechanism as the oxidative decomposition of 5-aminotetrazole.



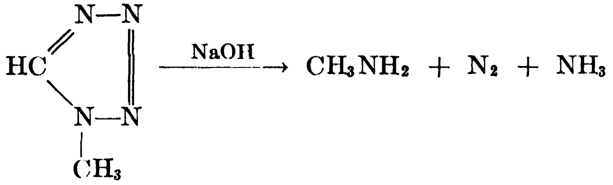
In the case of the alkaline decomposition of tetrazoles, the effect of negative substituents linked to the ring nitrogen atoms is to weaken the ring. While 5-phenyltetrazole is unchanged on heating with potassium hydroxide at 240°C. (91), 1-hydroxy-5-phenyltetrazole is ruptured by dilute alkali on warming (147).



Under the same conditions 1,1′-dihydroxyditetrazolyl-5,5′ is also decomposed.

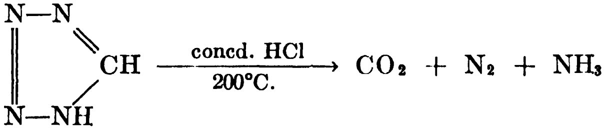


Heating 1-methyltetrazole with alkalies leads to the formation of nitrogen,

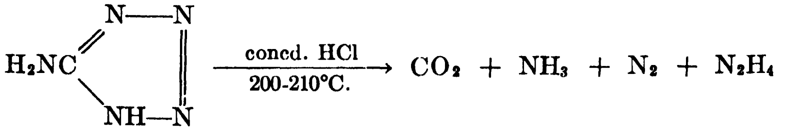


ammonia, and methylamine (81). Not enough compounds have been investigated to generalize concerning the limits of resistance of the tetrazole cycle toward alkali.

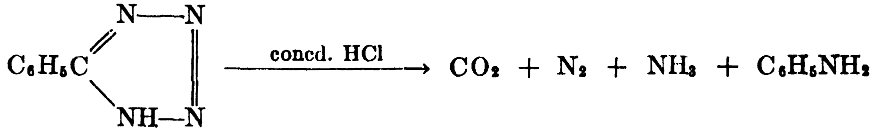
Most tetrazoles are stable toward acids at moderately elevated temperatures, but are decomposed by them above 200°C. Heating tetrazole at this temperature with hydrochloric or sulfuric acid results in the formation of carbon



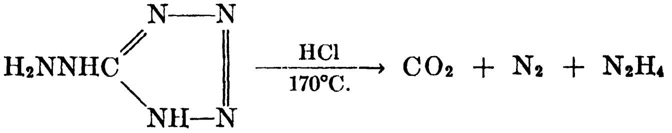
dioxide, ammonia, and nitrogen. If 5-aminotetrazole is heated with hydrochloric acid at 160-170°C., no splitting occurs; with the same reagent at 200-210°C. it is completely decomposed (139).



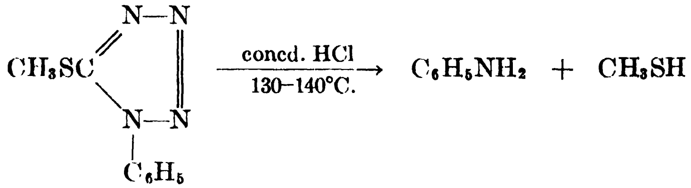
A similar decomposition is found in the case of 5-phenyltetrazole (91). The formation of hydrazine from 5-aminotetrazole and aniline from 5-phenyltetrazole



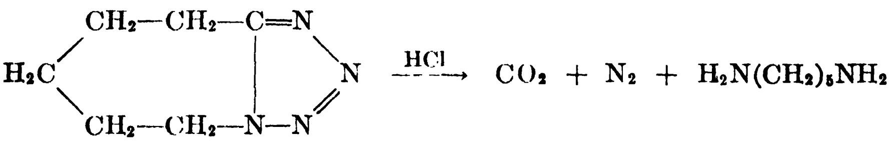
shows that a rearrangement has occurred, the group in the 5-position having become separated from carbon and attached to nitrogen. From the evidence it is impossible to indicate a satisfactory mechanism, but the similarity to the Beckmann rearrangement is apparent. Although 5-hydrazinotetrazole yields carbon dioxide, nitrogen, and hydrazine on heating at 170°C. with hydrochloric acid (139), it is possible that it decomposes in the same manner, since the product expected, triazane, would undoubtedly immediately decompose. Ditetrazolyl on warming with concentrated sulfuric acid yields nitrogen, ammonia, and carbon dioxide (85). The absence of cyanogen or other compound with linked carbon atoms from among the products of decomposition of ditetrazolyl constitutes further confirmation that the decomposition of 5-substituted tetrazoles by acid involves a separation of this group from the tetrazole carbon atom.



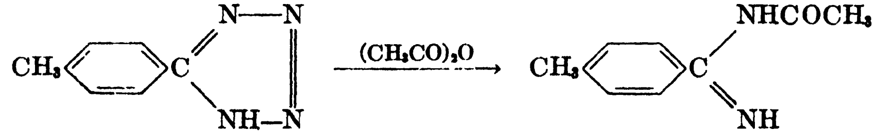
The observation that aniline and methyl mercaptan are formed from 1-phenyl-5-methylmercaptotetrazole by heating with concentrated hydrochloric acid (38) does not lead to a clear indication of the mode of decomposition. It does not appear, however, to be inconsistent with a mechanism involving preliminary separation of the CH_3S group.



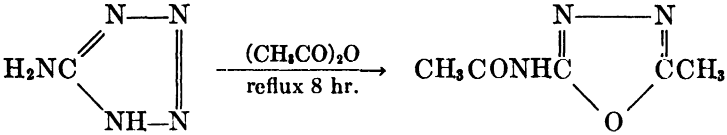
Heating metrazole with hydrochloric acid in a sealed tube gives rise to nitrogen, carbon dioxide, and pentamethylenediamine (101). The mechanism proposed by Schmidt for this decomposition involves preliminary formation of nitrogen and a pentamethyleneamine isocyanate, followed by hydrolysis of the cyanate group. In this case the group linked to the carbon of the tetrazole ring is also detached under the influence of acid.



Of considerable interest are the decompositions effected by acetic anhydride.



When 5-*p*-tolyltetrazole is heated with this reagent for half an hour, *N*-acetyl-*p*-toluamidine is produced (92, 93). Warming 5-aminotetrazole with acetic anhydride gently for a short time leads to the monoacetyl derivative; if instead, heating is continued for 8 hr., profound disintegration of the tetrazole ring occurs and 2-methyl-5-acetylamino-1,3,4-furodiazole is formed (111).



V. USES

Several patents have been issued covering the use of tetrazoles as explosives, either as initiators or as ingredients of initiating compositions. Thus Rathsburg described the use of salts of tetrazole, tetrazolyl azide, azotetrazole, diazoaminotetrazole, diazotetrazole, bistetrazole, and others for the purpose of replacing mercury fulminate in whole or in part in initiating explosives (96). The preparation of the copper salt of 5-nitrotetrazole for use in priming compositions is mentioned by Hertz (45), and the copper salt of diazoaminotetrazole is advocated by Brun (18).

The pharmacological uses of tetrazoles of the metrazole type depend on their ability to stimulate the central nervous system. Metrazole is extensively employed as a general cardiac and respiratory stimulant. Its use in the treatment of dementia praecox by shock therapy is also well known. Apparently metrazole is the best compound in this series for these purposes discovered to date, although others such as camphortetrazole (103) and trimethylenetetrazole (51) are claimed to have valuable properties.

Considerable doubt exists as to whether 5-sulfanilamidotetrazole has actually been prepared (52, 133, 141). No data appear to have been published on the bacteriostatic activity of the supposed sulfanilamidotetrazole. As an intermediate in an attempted preparation of this compound, Roblin and coworkers (97) prepared 5-*p*-nitrobenzenesulfonamidotetrazole. This compound attained a rather high blood level in spite of low water solubility, but was inactive as a bacteriostatic agent.

The author wishes to acknowledge his great debt to Dr. L. F. Audrieth for his encouragement and guidance at the inception of this work. Dr. Audrieth's stimulating enthusiasm for nitrogen chemistry was most infectious.

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THE CHEMISTRY OF THE PTERIDINES

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I. INTRODUCTION

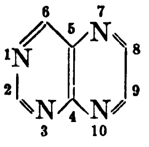
Knowledge of the pteridines[1] originated in the 1890's when Hopkins (30, 31, 32) published the results of his investigations on the wing pigments of the common English brimstone butterfly and the white cabbage butterfly. At about the same time, synthetic work by Kühling resulted in the first laboratory preparation of a substance with this nucleus (48). The relationship between these efforts was not clearly realized until 1940 (73, 74, 102), when the wing pigments, now known as "pterins" (88, 108), of the butterflies investigated by Hopkins were shown by Wieland and his collaborators to be derived from the pteridine ring system.

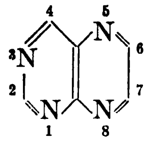
The recognition that one of the pterins, xanthopterin, occurs widely in animal organisms and bears some relationship, the nature of which is still obscure, to hematopoiesis, and the recent demonstration that folic acid, one of the newest members of the vitamin B complex and a substance of considerable therapeutic importance, contains this nucleus, have resulted in greatly increased interest in this class.

The pteridine ring system is composed of fused pyrimidine and pyrazine rings, illustrated in the accompanying formulas:

---

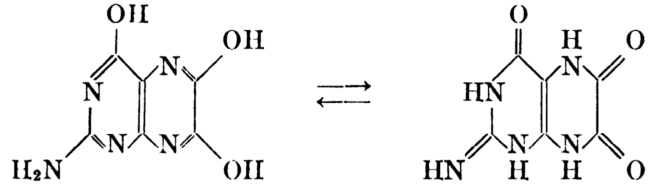
[1] The name "pteridine" appears first to have been applied to this ring system by Weygand (101; see also 81), but his publication has not been available to the author. The names alloxazine (48) (no longer suitable in the light of later work on alloxazines and isoalloxazines (49)), azine-purine (79), and lumazine (49) have also been proposed for compounds of this nucleus carrying two hydroxyl groups in the pyrimidine ring.


I


II

Its systematic name, according to the *Ring Index* (61), is pyrimido[4,5-*b*]pyrazine. The numbering shown in formula I, related to that used with the purines, is used exclusively in the extensive publications from German laboratories on the pterins, and has been adopted throughout this review, although the alternative numbering shown in II is preferred in the *Ring Index* and has been used in important American papers (2).

Most of the known pteridine derivatives have several hydroxyl or amino substituents and therefore possess manifold tautomeric possibilities, two of which are illustrated for leucopterin:

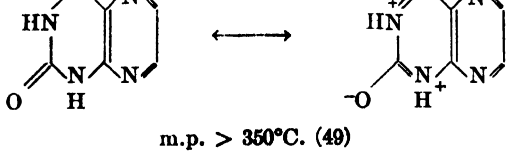

III IV

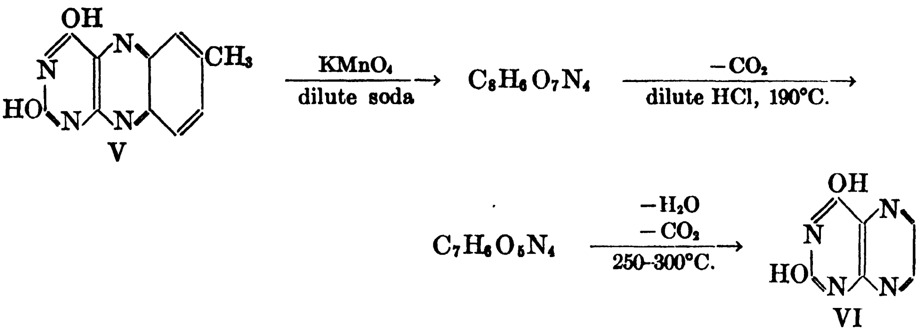
A choice between such tautomers cannot be made on the available evidence; in this article the "enolic" form with a completely aromatized system of double bonds, as illustrated in III, has arbitrarily been used in all systems where complete aromaticity is possible.[2]

II. SYNTHESIS OF THE PTERIDINE RING SYSTEM

A number of syntheses leading to derivatives of the pteridine nucleus have been described. The earliest successful synthesis of this ring system was carried out in 1895 by Kühling (48) who, having ascertained that the reaction of alloxan with aliphatic 1,2-diamines fails (47), was able to degrade "tolualloxazine" (V) by oxidative methods to 2,6-dihydroxypteridine (VI).

[2] The low solubilities in non-polar solvents and the high melting points exhibited almost without exception by these substances might be taken to indicate that the keto form, in which contributions from betaine-like structures are possible, predominates:


m.p. > 350°C. (49)

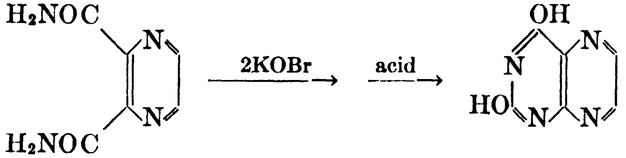


V

VI

Kühling noted the high stability of the ring system toward both acids and alkalies.

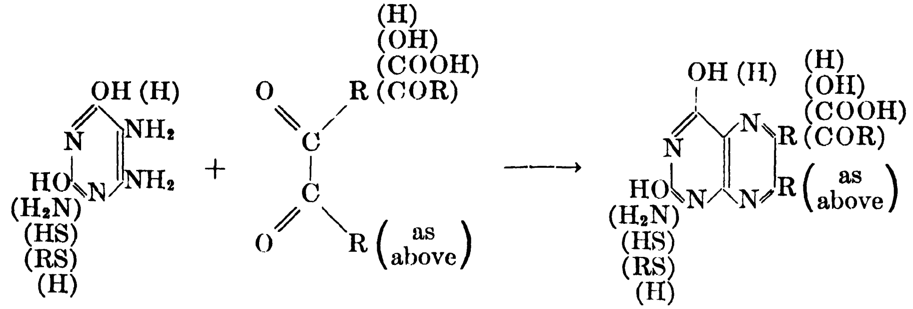
Another early synthesis yielding the same compound and, like the above, of only historical interest, was accomplished by Gabriel and Sonn (23), who obtained the potassium salt of 2,6-dihydroxypteridine by the action of 2 moles of potassium hypobromite on the diamide of 2,3-pyrazinedicarboxylic acid.



The smooth condensation of 1,2-dicarbonyl compounds with 4,5-diaminopyrimidines to yield derivatives of the pteridine nucleus was first systematically studied by Sachs and Meyerheim (79), although the reaction had previously been put to use for the characterization of diaminopyrimidines by Traube and his students (79) and by Isay (36). Sachs and Meyerheim showed that 3-methyl- and 1,3-dimethyl-2,6-dihydroxy-4,5-diaminopyrimidines condense smoothly with such varied dicarbonyl compounds as diacetyl, triketopentane, pyruvic and mesoxalic acids, alloxan, and also with ethyl dichloroacetate. 2,4,5-Triamino-6-hydroxypyrimidine, which was later to be of great value in the synthesis of the pterins, was used in one example. No attempt was made by Sachs and Meyerheim to assign structures to products resulting from unsymmetrical dicarbonyl compounds.

This reaction was also useful to Kuhn and Cook (49) and to Ganapati (24) in the synthesis of pteridines related to the flavines. Many examples of the condensation of 2,6-dihydroxy-4,5-diaminopyrimidine with 1,2-dicarbonyl compounds are given by them. Glyoxal, methylglyoxal, phenylglyoxal, diacetyl, β-naphthoquinone, phenanthrenequinone, benzil, 3,4,3′,4′-bis(methylenedioxy)benzil, dihydroxytartaric acid, camphorquinone, isatin, and alloxan were all used successfully. The reaction fails with *o*-benzoquinone (49), and Kuhn has pointed out that for the synthesis of alloxazines, only the condensation of alloxan with *o*-phenylenediamine is useful, in contrast to the pteridine series, where the analogous condensation between alloxan and aliphatic 1,2-diamines is unsuccessful (47, 110). Again, the structures of products from unsymmetrical dicarbonyl compounds were not ascertained.

The general reaction may be represented by the following equation:



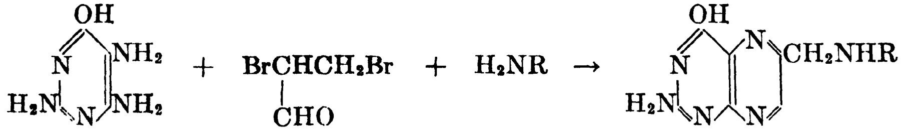
or tautomers with the ring nitrogens alkylated

or tautomers with the pyrimidine ring nitrogens alkylated

Many applications of this reaction and its modifications have been made recently in the pterin field, where the complicated and confusing structural picture resulting from degradative work was greatly clarified by Purrmann's synthesis of leucopterin in 1940 (73). More detailed accounts of syntheses in this field will be given later, and it is only necessary to say here that successful application of the above reaction, using (*1*) 2,6-dihydroxy-4,5-diaminopyrimidine, 2,4,5-triamino-6-hydroxypyrimidine, 2,4,5-triaminopyrimidine, and 2-hydroxy-4,5,6-triaminopyrimidine as diamine components, and (*2*) oxalic acid, ethyl mesoxalate, dichloroacetic acid, glyoxal, and glyoxylic acid as dicarbonyl components, has been achieved (2, 42, 73, 74, 75, 76, 77, 87, 104, 110).

Recently Polonovski and his coworkers (68, 70) and Wieland and Liebig (104) have extended the synthesis to 2-thiol-4,5-diaminopyrimidines and their thio ethers.

A further variation of this general synthesis consists in the use of α-halogen carbonyl compounds with 4,5-diaminopyrimidines. In this case, a dihydro compound is formed as an intermediate but is oxidized to the pteridine during the reaction (2). The important synthesis of the *Lactobacillus casei* liver factor, which will be discussed later, was of this type, and made use of 2,4,5-triamino-6-hydroxypyrimidine, α, β-dibromopropionaldehyde, and *p*-aminobenzoyl-*l*(+)-glutamic acid (2).



Note added in proof: Karrer and his coworkers (39a) have recently described the synthesis of pteridines carrying hydroxylated side chains in the 8(or 9)-position by the condensation of 2,4,5-triamino-6-oxypyrimidine with both aldoses and ketoses.

III. PHYSICAL PROPERTIES OF THE PTERIDINES

The simple pteridine nucleus is unknown, but those derivatives which have been studied, containing functional groups (hydroxyl, amino, or sulfhydryl) in the 2- and 6-positions (pyrimidine ring) and functional groups or alkyl and aryl groups in the 8- and 9-positions (pyrazine ring), are virtually all very high-melting substances of sparing solubility in the ordinary organic solvents and in cold water, although polyhydroxy compounds such as ethylene glycol and glycerol appear to have some solvent power (33, 82).

The ultraviolet and visible light absorption of the pteridines has been thoroughly studied (7, 13, 22, 39, 49, 71, 82) and strongly resembles that of the flavines and alloxazines (7, 50). Simple derivatives carrying functional substituents only in the 2- and 6-positions are yellow; those substituted in the pyrazine ring may be yellow or colorless according to the number and position of the substituents.

One of the most striking characteristics of the pteridines is their strong fluorescence, which is similar to that of the flavines (50). Even the simple members exhibit this tendency so strikingly that Kuhn proposed the generic name "lumazine" for 2,6-dihydroxypteridines (49). The nuance of the fluorescence varies from compound to compound, and in any one compound it may vary characteristically with pH. For example, in strong solutions of mineral acids xanthopterin shows a strong red fluorescence under ultraviolet light (3, 40), while at pH's from 7 to 11 the fluorescence is sky blue (40). Sensitive microchemical tests based on fluorescence and adsorption behavior have been developed for the recognition of small amounts of pterins in insects and in other biological materials (3, 17, 40, 104; see also 39, 55, 62, 66, 69).

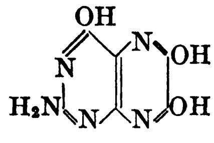
Polonovski and his coworkers (68, 70, 71), during synthetic studies on sulfur-containing pteridines, have observed that 2-thiol-6-hydroxypteridines do not fluoresce, whereas the corresponding 2-ethylthio ethers possess strong blue or green fluorescence similar to that of the 2,6-dihydroxypteridines. Moreover, the 2-thiol compounds inhibit the fluorescence of the corresponding thio ethers.

The lack in the pterins of the usual criteria for identity has led to rather widespread use of DeBye–Scherrer diagrams for this purpose by Schöpf (83) and by Wieland and his collaborators (106; and later papers); such diagrams are available for a number of natural and synthetic pteridine derivatives. The x-ray diagram of leucopterin has also been studied from the structural point of view without conclusive results (56).

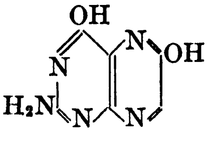
IV. CHEMICAL PROPERTIES OF THE PTERIDINES

A. GENERAL CHEMICAL PROPERTIES

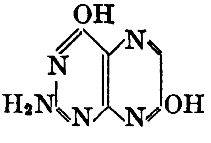
Much of our knowledge of the general chemistry of the pteridines has resulted from structural studies carried out on the naturally occurring pterins by European workers, and the two most important pterins, leucopterin (VII) and xanthopterin (VIII), together with isoxanthopterin (IX) will figure prominently in the following discussion.



VII
Leucopterin



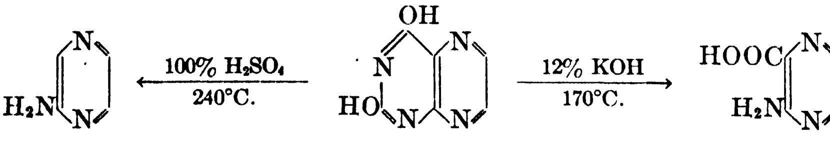
VIII
Xanthopterin



IX
Isoxanthopterin

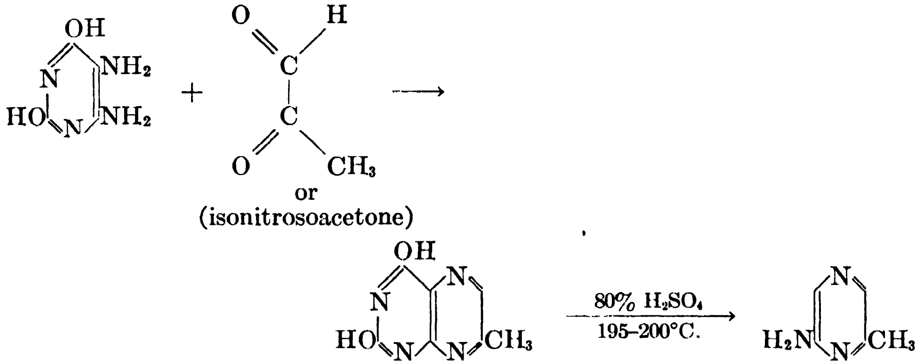
Virtually all the pteridines have well-developed acidic properties and are soluble in both alkalies and ammonia (13, 23, 24, 48, 49, 105, 108). Quantitative data are available for only two compounds, 2-amino-6-hydroxypteridine, whose pK_a is 8.0, and 2-amino-6-hydroxy-8-pteridinecarboxylic acid, whose pK_a's are 3.9 and 7.7, respectively, for the first and second dissociations (2). The presence of an amino group in the 2-position confers basic properties as well, although the substituents present in the pyrazine ring and their positions markedly affect the degree of basicity. For example, leucopterin (VII), with two hydroxyl groups in the 8- and 9-positions, is nearly devoid of basic properties, resembling uric acid in this respect (105). It does form a yellow sulfate in fairly concentrated sulfuric acid (104). On the other hand, xanthopterin (VIII), carrying a hydroxyl in the 8-position, has rather pronounced basic properties. Isoxanthopterin (IX), differing from xanthopterin only in the position of the hydroxyl in the pyrazine ring, is significantly less basic than xanthopterin (75) and is also colorless, as is leucopterin, whereas xanthopterin is yellow. Purrmann has discussed the theoretical basis for these differences in terms of inductive effects (75).

Simple pteridine derivatives carrying hydroxyl groups only on the pyrimidine ring are very stable towards hydrolysis (48), but under appropriate conditions degradation of the pyrimidine ring occurs with either acids or bases (100). For example, 2,6-dihydroxypteridine (X), heated with 100 per cent sulfuric acid to 240°C., gives 2-aminopyrazine in high yield. Homologs give lower yields however, and optimum results with homologs are obtained with somewhat more dilute acid and lower temperatures. The same compound is degraded by heating with 2 to 3 equivalents of 12 per cent alkali for 2 hr. at 170°C. to 2-aminopyrazine-3-carboxylic acid in 93.5 per cent yield. With stronger alkali or longer heating, some of the corresponding 2-hydroxy compound is produced, although higher homologs yield only the amino compound (19, 100).



X
2,6-Dihydroxypteridine

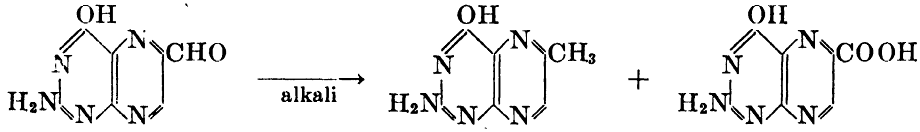
These degradations were developed during a search for better methods for preparing 2-aminopyrazines and in addition to the above example have been applied to 8- or 9-methyl-, 8 or 9-phenyl-, 8,9-dimethyl- and 8,9-diphenyl-2,6-dihydroxypteridines. From the monomethyl compound (XI) an aminomethylpyrazine not identical with 2-amino-5-methylpyrazine and therefore presumably 2-amino-6-methylpyrazine (XII) was obtained. This implies that the monomethyl compound is 2,6-dihydroxy-9-methylpteridine and that the synthesis used in its preparation proceeds as follows (100) (see page 65):



XI XII

8-Alkyl-2-amino-6-hydroxypteridines are converted to the corresponding carboxylic acid on oxidation with hot alkaline permanganate (2). The acid may be decarboxylated by heating to 300°C. to yield the parent 2-amino-6-hydroxypteridine (2).

An interesting dismutation is undergone by 2-amino-6-hydroxy-8-pteridinealdehyde (XIII) on standing in alkaline solution in the absence of oxygen. Under these conditions, the aldehyde is converted into a mixture of the 8-methyl derivative (XIV) and the 8-carboxylic acid (XV) (2).

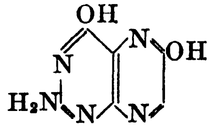


XIII XIV XV

2,6-Dihydroxy-8,9-diphenylpteridine reacts with diazomethane to yield a dimethyl derivative of unknown structure (24).

B. XANTHOPTERIN, ISOXANTHOPTERIN, AND LEUCOPTERIN

These three naturally occurring substances are by far the best-characterized pteridine derivatives. In spite of their structural similarity, they differ strikingly in chemical behavior.



XVI
Xanthopterin

Xanthopterin (XVI) is a yellow solid melting above 400°C., which is obtained crystalline with difficulty (82, 108). It is very slightly soluble in the ordinary organic solvents and in cold water, although hot ethylene glycol (33) and warm glycerol (82) dissolve it, and it is freely soluble in hot water (29). It is amphoteric, behaving both as a base and as a weak dibasic acid, and its beautifully crystalline barium salt (called "β-xanthopterin barium salt" when prepared under controlled conditions) (82) is particularly suitable for purification and characterization (108). Partial hydrolysis of the barium salt occurs on crystallization from water, and it must be recrystallized from half-saturated barium hydroxide (82). The sodium and potassium salts can be obtained crystalline but in poor yield, and amorphous silver, gold, lead, and palladium salts are known (42, 82).

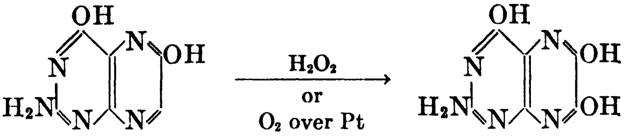
In contrast to leucopterin, the basic properties of xanthopterin are well developed, and it is readily soluble in dilute mineral acids from which it may be precipitated by sodium acetate (108). It appears to be nearly completely ionized in anhydrous formic acid, since its molecular weight in this solvent is about one-half of the nominal value (85).

With sulfurous acid, either xanthopterin or its barium salt forms a colorless crystalline adduct from which it may be regenerated by either acid or alkali (106). It gives a murexide test (29, 30, 108) but is more stable to dilute nitric acid than is uric acid (108).

Xanthopterin, like xanthine, couples with diazotized 2,5-dichloroaniline (82). Similarly, the substance prepared by Sachs and Meyerheim from 4,5-diamino-2,6-dihydroxy-1,3-dimethylpyrimidine and dichloroacetic ester, which presumably has the same configuration in the pyrazine ring as xanthopterin, couples with diazotized nitroaniline (79), and the ability to couple may be a general characteristic of 8-hydroxypteridines.

Nitrous acid readily attacks xanthopterin but unlike leucopterin, which yields the corresponding 2-desamino compound, the whole molecule is disrupted. Neither sodium nitrite and sulfuric acid nor nitrosylsulfuric acid in concentrated sulfuric acid lead to desaminoxanthopterin (85), which can, however, be prepared synthetically. It is colorless and less basic than xanthopterin (104). In the Van Slyke determination, xanthopterin loses 34 per cent of its nitrogen as gaseous nitrogen (41).

A variety of oxidizing agents attack xanthopterin readily. Its behavior toward hydrogen peroxide is particularly interesting. With perhydrol in acetic acid at room temperature, a colorless peroxide is produced which reverts to xanthopterin on treatment with alkali or on heating in aqueous suspension (106). The peroxide will oxidize iodide ion to iodine (106), and both it and xanthopterin on standing for several days at room temperature with an excess of perhydrol are converted into leucopterin (106, 107). On heating with excess perhydrol the peroxide yields melanurenic acid (106), and it has also been possible to isolate 2-iminooxonic acid in low yield as a result of the action of hydrogen peroxide on xanthopterin (107). The conversion of xanthopterin to leucopterin may also be carried out in 63 per cent yield by the use of molecular oxygen over platinum (107).



Hopkins' early observation that crude xanthopterin could be oxidized to "uric acid" by warm dilute nitric acid was considered by Schöpf (83) to have been merely the result of solution of the xanthopterin present as its nitrate (colorless). This would leave the contaminating non-basic leucopterin behind. That this would result with xanthopterin containing leucopterin as an impurity cannot be denied, but in view of the ease with which xanthopterin can be oxidized to leucopterin, Hopkins' observation perhaps merits reconsideration.

Xanthopterin is rapidly attacked by sodium chlorate in hydrochloric acid solutions at 100°C. with the formation, through transient intermediates, of oxalic acid, glyoxylic acid, guanidine, and urea, but no alloxan. At 80°C., oxalylguanidine can be isolated (85). 2,4,5-Triamino-6-hydroxypyrimidine yields oxalylguanidine and oxalic acid under the same conditions, and the isolation of these substances was taken by Schöpf to indicate the presence in xanthopterin of a 2-aminopyrimidine ring (85).

Ozone rapidly attacks xanthopterin, yielding oxalic acid, oxalylguanidine, and guanidine (85).

A variety of reducing agents readily transform xanthopterin into a colorless leuco compound, dihydroxanthopterin. Zinc dust in either acid or alkali (108), fuming hydriodic acid (110), either sodium sulfite or sodium hydrosulfite in neutral solutions (40), glutathione in neutral solutions (40), and hydrogen sulfide in neutral or alkaline solutions (40) will bring about this reduction. The reaction is at least partially reversible, and dihydroxanthopterin, prepared either by reduction of leucopterin with sodium amalgam (92) or by decarboxylation of dihydroxanthopterincarboxylic acid (75), can be converted to xanthopterin in 83 per cent yield by molecular oxygen over platinum (75) or in good but unspecified yield by oxidation with alkaline silver solutions (92). According to Koschara (41), when hydrogen sulfide is used to reduce xanthopterin, a sulfur-containing substance is formed in part, and catalytic reduction is not entirely reversible, since when dihydroxanthopterin solutions prepared in this way are shaken with air and then again reduced catalytically, only about 50 per cent of the original hydrogen is taken up.

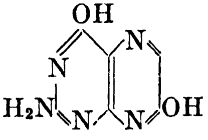
Dihydroxanthopterin and its sulfate can both be obtained crystalline (75, 110). It reduces hypobromite, Chloramine T, quinone, methylene blue, and 2,6-dichlorophenolindophenol, in addition to the reagents mentioned above (92).

An interesting difference in the ease of decarboxylation between xanthopterincarboxylic acid and its colorless dihydro derivative has been observed. The former cannot be decarboxylated, but the latter readily yields dihydroxanthopterin by loss of carbon dioxide (75).

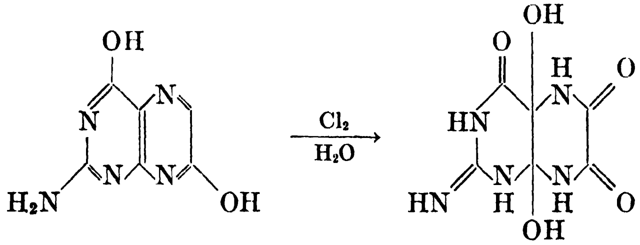
Xanthopterin is stable towards dilute hydrochloric acid and may be concentrated with it many times (108). Energetic acid hydrolysis of xanthopterin or its barium salt produces glycine, isolated as hippuric acid, in 40–45 per cent yield. The yield may be raised to 56–59 per cent by preliminary reduction to dihydroxanthopterin. Under the same conditions, 2,4,5-triamino-6-hydroxypyrimidine, guanine, and uric acid give hippuric acid in 58–67 per cent yield (84).

Short hydrolysis with strong potassium hydroxide does not affect xanthopterin, although on continued hydrolysis with barium hydroxide a mole of ammonia is slowly lost (82).

Isoxanthopterin (XVII) (8-desoxyleucopterin) differs strikingly from xanthopterin. It is colorless, significantly less basic, and dissolves in fuming hydriodic acid with the formation of a dihydro compound and the precipitation of 2 equivalents of iodine. On dilution of the solution, the iodine is reduced and isoxanthopterin reprecipitates (75, 110). Xanthopterin likewise is reduced by fuming hydriodic acid, but the dihydro compound is not immediately reoxidized on dilution.[3] A further difference is shown by the corresponding



XVII
Isoxanthopterin



XVIII
Leucopterin glycol

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[3] The extraordinary behavior of isoxanthopterin toward fuming hydriodic acid may be a consequence of its low basicity. Presumably the following equilibria are set up:

$$\text{Isoxanthopterin} + \text{HI} \rightleftarrows \begin{matrix}\text{Isoxanthopterin}\\ \text{hydroiodide}\end{matrix} \underset{\text{I}_2}{\overset{2\text{HI}}{\rightleftarrows}} \begin{matrix}\text{Dihydroisoxanthopterin}\\ \text{hydroiodide}\end{matrix}$$

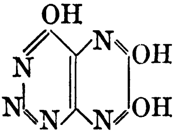
$$\text{Xanthopterin} + \text{HI} \rightleftarrows \begin{matrix}\text{Xanthopterin}\\ \text{hydroiodide}\end{matrix} \underset{\text{I}_2}{\overset{2\text{HI}}{\rightleftarrows}} \begin{matrix}\text{Dihydroisoxanthopterin}\\ \text{hydroiodide}\end{matrix}$$

In fuming hydriodic acid, both substances dissolve as hydroiodides, and both series of equilibria are displaced toward the right, whereas in dilute hydriodic acid, isoxanthopterin, being much less basic, precipitates as the free base, and the equilibrium in this case is shifted toward the left, even if the values of the equilibrium constants for the two redox reactions are similar.

carboxylic acids. Isoxanthopterincarboxylic acid, in contrast to xanthopterincarboxylic acid, is readily decarboxylated in high yield by heating to 260°C. (75).

Isoxanthopterin reduces Tollens' reagent and phosphotungstic acid, gives a murexide test, and forms yellow sodium and silver salts (105). In contrast to xanthopterin, it cannot be converted to leucopterin by oxidation, although on treatment with chlorine water, leucopterin glycol (XVIII) is formed. Oxalylguanidine may also be isolated from this reaction (103).

Leucopterin (XIX) is a colorless crystalline solid of high melting point. It is distinctly acidic, dissolving readily in dilute alkalies and ammonia (105). Its yellow monopotassium salt is particularly characteristic and serves for purification (87). In contrast to uric acid, which reduces silver salts to metallic silver, leucopterin yields a bright yellow silver salt with silver nitrate (88). It is, however, superficially very similar to uric acid, and was mistaken for this substance by early workers (31, 111).



XIX

It exhibits only the feeblest basic properties (105), although it is possible to prepare a yellow sulfate in fairly concentrated sulfuric acid (104). It is insoluble in fuming hydriodic acid and may be separated from isoxanthopterin by making use of this property (110).

Leucopterin gives the murexide test, yielding a somewhat bluer tone than uric acid (88, 105).

A monoacetyl derivative of unknown structure is produced by the action of acetic anhydride and sulfuric acid on leucopterin. The acetylation does not proceed in pyridine or with acetic anhydride alone, and benzoylation fails both in pyridine and in sulfuric acid (105).

Leucopterin is desaminated by treatment with sodium nitrite in fairly concentrated sulfuric acid to give 2,6,8,9-tetrahydroxypteridine (desaminoleucopterin)[4] (105). Isoleucopterin (6-amino-2,8,9-trihydroxypteridine) is not desaminated by nitrous acid (104) nor is isoguanine, a purine in which a similar arrangement of hydroxyl and amino groups is present in the pyrimidine ring (21).

The action of phosphorus pentachloride and phosphorus oxychloride on leucopterin produces a monochloro derivative (XX) which can be hydrolyzed to leucopterin by alkalies (105). The chlorine of this leucopteryl chloride occupies the 6-position, since it is reduced by hydriodic acid to 6-desoxyleucopterin (XXI), which has been synthesized by the condensation of 2,4,5-triaminopyrimidine with oxalic acid (110).

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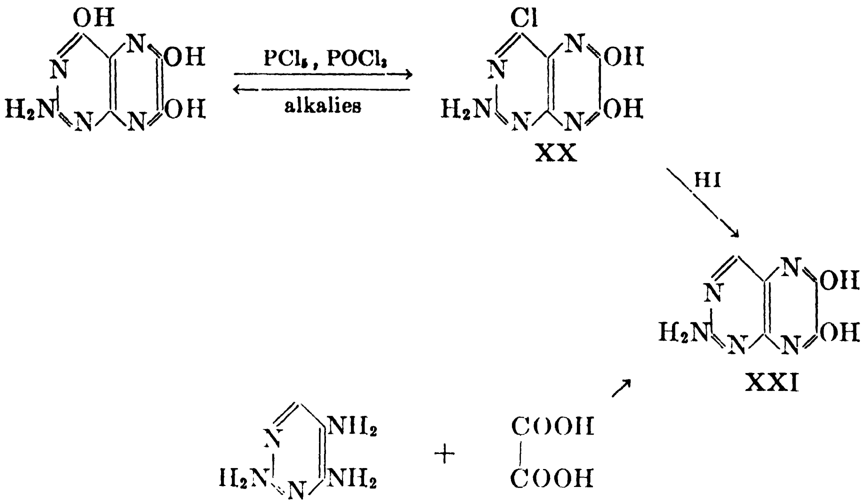
[4] In accordance with the arbitrary use of aromatized formulas see page (64) this substance will be referred to in this review as "desaminoleucopterin."



Under the conditions which produce leucopteryl chloride from leucopterin, desaminoleucopterin yields a dichlorodihydroxypteridine, probably 2,6-dichloro-8,9-dihydroxypteridine,[5] but if alkali is avoided in working up the product, the corresponding tetrachloro compound results. This tetrachloropteridine reverts to the dichloro compound on treatment with 0.75 *N* sodium hydroxide at 80°C., and to desaminoleucopterin with 25 per cent sodium hydroxide at 140°C. With dry ammonia in ether, a monoaminotrichloropteridine is formed (87). The rather remarkable lability of the chlorine atoms in the 8- and 9-positions suggests that methyl groups in similar positions will be found to exhibit the characteristic reactivity in condensation reactions that is shown by methyl groups in other aromatic systems whose corresponding halogen derivatives are similarly active (2,4-dinitrotoluene and 2,4-dinitrochlorobenzene; α-picoline, α-chloropyridine; etc.). These positions, in the unsubstituted nucleus, may by similar reasoning be expected to be subject to fairly easy nucleophilic substitution.

Leucopterin does not react with diazomethane in dry ether (102, 105) but if aqueous methanol is added, nitrogen is evolved and two isomeric trimethyl derivatives are produced, one of which was of considerable importance in structural studies of the pterins, since it is soluble enough to allow molecular-weight determinations in phenol (102). Desaminoleucopterin yields a tetramethyl derivative under the same conditions (102).

Pure leucopterin does not reduce phosphotungstic acid nor alkaline silver solutions (104), although earlier reports (88, 105), based on experiments with natural leucopterin probably containing uric acid, indicated that weak reduction of both occurred. It is attacked by alkaline ferricyanide (105), but in contrast to uric acid is unaffected by molecular oxygen in the presence of manganese dioxide (105).

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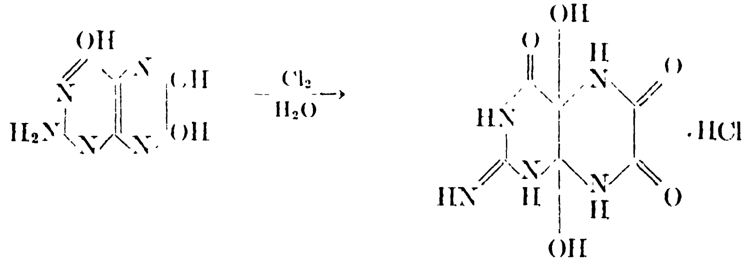
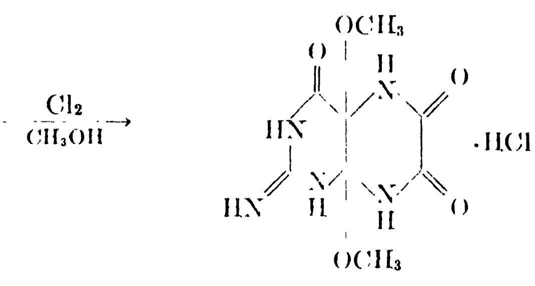
[5] This structure was favored by Schöpf (87), primarily because the chlorine atoms in the analogous 4,5-diamino-2,6-dichloropyrimidine are stable to hydrolysis. The character of such chlorine atoms may be entirely altered, however, by the conversion of two primary amino groups to two tertiary ring members, and the structure of this substance cannot be considered firmly established.

Like uric acid, leucopterin is attacked at the juncture of the two rings by chlorine in methanol or by chlorine water. In methanol, the hydrochloride (XXIII) of leucopterin glycol dimethyl ether results, although this substance has not been obtained pure because of its ready loss of one methyl group by hydrolysis. The corresponding free base can be obtained from the hydrochloride by the action of pyridine in methanol (105). In water, the hydrochloride (XXII) of leucopterin glycol itself is obtained, along with a small amount of oxalylguanidine, the yield of which can be increased by working at 60–70°C. (102, 103, 105). Leucopterin glycol can be obtained from the hydrochloride by treatment with pyridine or by precipitating it as its double salt with mercuric acetate, followed by removal of mercuric ion by hydrogen sulfide (105).

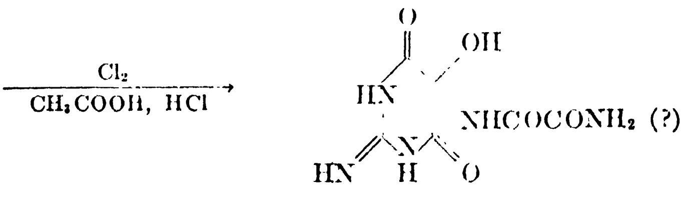
Leucopterin in suspension in acetic and hydrochloric acids on treatment with chlorine yields a product whose constitution has not definitely been established, but which may be 2-imino-5-hydroxyuramil-7-oxamide (XXIV), analogous to 5-hydroxypseudouric acid (107). Similarly, desaminoleucopterin, on treatment



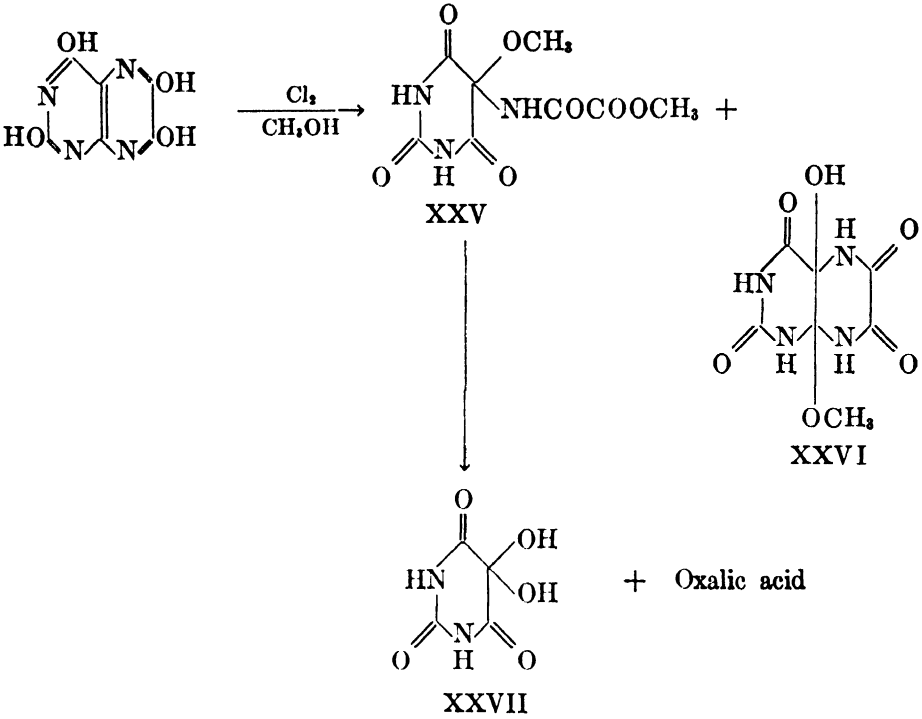
XXII



XXIII



XXIV

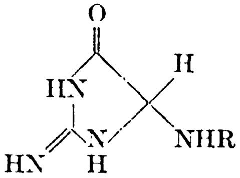


with chlorine in methanol, gives principally 5-methoxyuramil-7-oxalic acid methyl ester (XXV), although a small amount of the glycol half-ether (XXVI) corresponding to leucopterin glycol half-ether is also produced (109). On hydrolysis, the ester gives oxalic acid and alloxan (XXVII) (109).

Both leucopterin glycol and its diether are much less stable toward hydrolysis than leucopterin itself. The diether on warming in aqueous solution readily loses methanol, and further hydrolysis produces carbon dioxide and a small amount of guanidine, but no oxalic acid or ammonia. It is possible to isolate from the hydrolytic mixture by means of its double salt with mercuric chloride an acid $C_4H_5O_4N_2(OCH_3)$ which forms a crystalline methyl ester with diazomethane (105). Its constitution is not known with certainty, but it yields glyoxylic acid on alkaline hydrolysis and oxalic acid on acid hydrolysis and may have the accompanying structure (105):

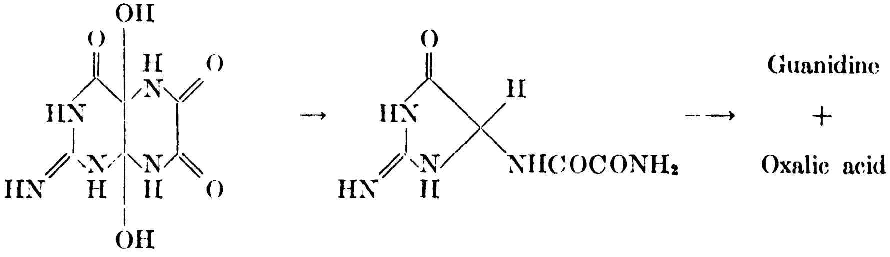
$$NH_2COCH(OCH_3)NHCOCOOH$$

Leucopterin glycol is stable to boiling water (103) but on energetic hydrolysis with dilute acids it yields carbon dioxide, acid ammonium oxalate, and guanidine, isolated as its chloroaurate (105). Apparently the pyrimidine ring is in part altered before the liberation of guanidine, since only about one third of a mole of guanidine, which is stable under these conditions, is isolable (105). With excess alkali, the glycol is degraded in the cold, carbon dioxide is split off, and it is possible to isolate 2-iminohydantoin-5-oxamide (XXVIII), the corresponding oxamic acid (XXIX), 2-imino-5-aminohydantoin (XXX) (103, 107), and oxalic acid (105).

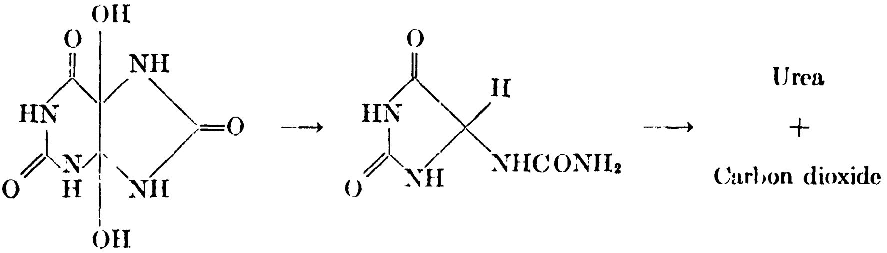


XXVIII : $R = COCONH_2$
XXIX : $R = COCOOH$
XXX : $R = H$

The degradation of leucopterin glycol (XXXI) is thus entirely analogous to that of uric acid glycol (XXXII) (81).



XXXI



XXXII

Guanidine can likewise be detected after treatment of 2-amino-6-hydroxy-8-pteridinecarboxylic acid with chlorine water and hydrolysis (2).

Leucopterin itself is completely degraded to carbon monoxide, carbon dioxide, ammonia, and glycine by vigorous acid hydrolysis (105).

The ordinary reducing agents do not attack leucopterin (105), although it has been possible to convert it in good yield into a mixture of xanthopterin and dihydroxanthopterin by making use of sodium amalgam (92), and this reaction is employed in what appears to be the most convenient synthesis of xanthopterin. Electrolytic reduction of leucopterin produces a small amount of isoxanthopterin but no xanthopterin (104).

V. THE PTERINS[6]

A. GENERAL REMARKS ON THE PTERINS

As early as 1871 Meldola (quoted in reference 31) called attention to the fact that the yellow pigment in the wings of the common English brimstone butterfly (*Gonopterex rhamni*) was soluble in water. During the years 1889-93 F. Gowland Hopkins undertook a study of the wing pigments of the Pierids (29-32). He was able to isolate the white wing pigment of European cabbage butterflies (*Pieris brassicae*) in crystalline form, but mistook it for uric acid, to which it shows many superficial similarities. He also studied the yellow pigment from the wings of brimstone butterflies and showed that a similar red pigment occurs in certain other butterflies. The white, yellow, and red pigments all occur in the wing scales, and in this respect differ from a green pigment occurring between the chitin layers, later shown to be a chromoprotein whose blue prosthetic group is related to the bile pigments.

After a lapse of over thirty years Wieland and his collaborators undertook the study of these pigments. They were successful in isolating the yellow pigment of brimstone butterflies, which they named "xanthopterin," and its barium salt in pure crystalline state (108); shortly thereafter they demonstrated that the white pigment of cabbage butterflies which they called "leucopterin," while indeed similar to uric acid, differed from it in a number of ways (88). Continued work with these and other pierids by both Wieland and by Schöpf and their collaborators led to the isolation of several other pigments, of which isoxanthopterin (desoxyleucopterin) (105), formerly called "anhydroleucopterin," and erythropterin (83), the red pigment also observed by Hopkins, are the best characterized. The former accompanies leucopterin in small amounts in the wings of cabbage butterflies, and the latter accompanies xanthopterin in varying amounts in orange and red pierids. Several purine derivatives were also observed, among them uric acid (91), xanthine (72), hypoxanthine (91), and isoguanine, which was at first thought to be a pterin and was called "guanopterin" (83).

Of the pterins, xanthopterin is by far the most widespread in nature. Its color, fluorescence, and adsorption characteristics render it particularly easy to identify in small amounts (3). It occurs in insects of several other orders beside the lepidoptera, although only in a few species. Koschara (40) has shown that in small amounts it is a normal constituent of urine, both animal and human, and that it occurs in other animal sources but apparently not in plants (42). It has also been detected in the crab *Cancer pagurus* (69).

The occurrence of leucopterin appears to be limited to insects. In addition to being present in both white and colored pierids (32, 78, 83, 88), it occurs in wasps (83) and is thus, like xanthopterin, not limited to the lepidoptera. It does not occur in human urine, guano, or snake excrement (17, 104).

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[6] An excellent account of chemical work in the pterin field has been given by Schöpf (81).

It is remarkable that whereas the pterins appear to be end-products of protein metabolism laid down by the chrysalis during metamorphosis (104), no pterins appear in the excreta of adult insects which carry them as pigments (3, 105), although much uric acid is found.

Several other substances which are less well characterized than the simple pterins but which appear to be related to them have been isolated from widely differing sources. Koschara has obtained from human urine a sulfur-containing substance, $C_{11}H_{13}O_3N_5S_2$, which he has named urothione and whose absorption spectrum indicates the presence of a pteridine nucleus, although it gives no murexide test. It is optically active, contains a terminal glycol group revealed by periodic acid oxidation, and yields a tetraacetate in which one acetyl group is attached to nitrogen (43, 44). Polonovski and his coworkers have isolated by acid extraction of carp scales a substance, fluorescyanine, which may be related to the pterins. It contains less nitrogen, appears to be more soluble in organic solvents, and may be separated from riboflavin, with which it usually occurs, by chromatographic adsorption (66). Finally, fluorescent substances whose chemical and spectroscopic properties are similar to those of xanthopterin have been isolated from fluorescent bacteria (25), from the eyes of dogfish and alligators (62), and from the hepatopancreas of crabs (69).

B. STRUCTURAL DETERMINATION AND SYNTHESES

Much of the chemical work leading to the elucidation of the structure of the pterins has already been discussed in the preceding section, and it will be necessary here only to give a brief account of how these observations were used in the structural studies. The preceding section, however, gave no inkling of the difficulties[7] encountered by Wieland, Schöpf, and their coworkers during the course of this work. The pigments are all quite sparingly soluble in organic solvents and are difficult to purify. The ordinary criteria of purity and identity are lacking, since the pterins are all very high melting. In addition to retaining water of crystallization tenaciously, they burn with difficulty in both carbon hydrogen and Dumas nitrogen analyses. To point out that in spite of continuing work since 1925, the correct molecular formulas of the three most important pterins were not known with certainty until 1941 (102), when the first reliable molecular-weight determination was carried out on a derivative of leucopterin, is merely to emphasize the difficulties encountered in the characterization of these substances.

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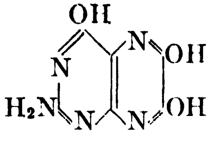
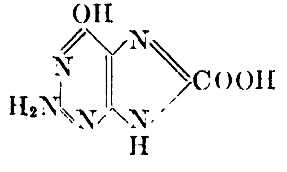
[7] No inconsiderable part was the collection of enough insects to insure reasonable quantities of material with which to work. A large number of cabbage butterflies were collected by school children during the summers of 1930–32 under the supervision of their teachers at the inducement of the Bavarian Ministry of Education, and a considerable number were also obtained from the Freiburg region. Around 200,000 insects were thus made available to Wieland and his collaborators at an early stage of the work (105). Schöpf and Kotler (85) used 16,000 of the large yellow South American Pierid, *Catopsila rurina*, in their study of xanthopterin, and Tartter (91) has reported results obtained during a study in which 850,000 insects (mixed Pierids) were used. Hopkins' work in this field was constantly hampered by scarcity of material (33).

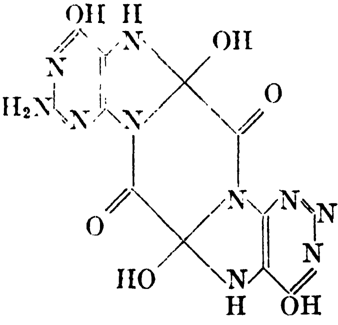
Early hypotheses (88, 108) as to the structures of leucopterin and xanthopterin, which postulated a basic structure made up of two 2,6-dioxypurine rings joined through the 8-positions, corresponding to $C_{10}H_{10}O_6N_8$ and $C_{10}H_{10}O_4N_8$ for these substances, were discarded when it was shown that guanidine could be obtained by chlorine–methanol oxidation of leucopterin, followed by hydrolysis of the resulting glycol ether (105). The analyses then available (82, 105) corresponded most closely to the formulas $C_{19}H_{19}O_{11}N_{15}$ for leucopterin and $C_{19}H_{19}O_7N_{15}$ for xanthopterin, although in 1936 that of xanthopterin was revised, on the basis of further analyses of its barium salt, to $C_{19}H_{18}O_6N_{16}$. Only after it had been demonstrated (106, 107) that xanthopterin could be oxidized to leucopterin by hydrogen peroxide or by molecular oxygen over platinum[8] was it apparent that the earlier analytical data were faulty. More rigorous drying (170°C. in vacuum) of leucopterin was then found to yield material whose analyses agreed with the formula $C_{18}H_{15}O_9N_{15}$ (or $C_6H_5O_3N_5$), forcing a revision of the empirical formula of xanthopterin to $C_{18}H_{15}O_6N_{15}$ (or $C_6H_5O_2N_5$) (107). At the same time, it was recognized that certain degradation products of leucopterin, obtained by careful alkaline hydrolysis of leucopterin glycol, which at an earlier time were thought to have contained 13, 14, and 15 carbon atoms (103), were in fact much simpler, and contained no more than five carbon atoms. Continued consideration of the trimeric formulas was therefore unnecessary (107). The demonstration by Purrmann (73) in 1940 that leucopterin can be synthesized in high yield from 2,4,5-triamino-6-hydroxypyrimidine and oxalic acid then limited the possible structures for this substance to XXXIII, XXXIV or, less probably, the dimeric modification of the latter, XXXV.



XXXIII



XXXIV



XXXV

A choice between the first two of the above structures was made possible by Purrmann's observation (74) that the substance XXXVI, prepared from 4,5-

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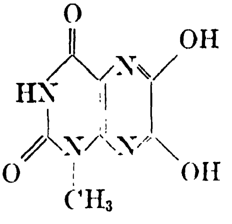
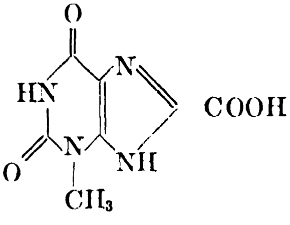
[8] As early as 1933 Schöpf had suggested that leucopterin might be an oxidation product of xanthopterin (82).

diamino-2,6-dihydroxy-3-methylpyrimidine and oxalic acid by his procedure, is not identical with Traube's (97) 3-methyl-8-xanthinecarboxylic acid (XXXVII), which is easily decarboxylated in contrast to Purrmann's compound and to leucopterin both of which are very stable to heat. Further evidence in favor of the pyrimidinopyrazine structure was obtained by Schöpf (87), who converted desaminoleucopterin to a tetrachloropteridine by the action of phosphorus pentachloride, a reaction difficult to interpret on the basis of the 8-carboxypurine structure.



XXXVI



XXXVII

The dimeric formulation was finally definitely excluded by the preparation (102) of two isomeric trimethyl derivatives of leucopterin by the action of diazomethane in the presence of aqueous methanol, one of which in phenol provided the first reliable molecular-weight determination in an indifferent solvent in the entire pterin field.

Syntheses of xanthopterin and isoxanthopterin (8-desoxyleucopterin) by Purrmann (74, 75) completed the structural elucidation of the three well-characterized simple pterins. The condensation of 2,4,5-triamino-6-hydroxypyrimidine with dichloroacetic acid at 120°C. yielded the intermediate 5-dichloroacetylamino-2,4-diamino-6-hydroxypyrimidine, whose silver salt when heated with silver carbonate cyclized to xanthopterin. The over-all yield was only 6 per cent, principally because of the poor conversion in the last step (74). The structure of the intermediate acylated pyrimidine, on which the structure of xanthopterin rested,[9] was assigned on the basis of the known reactivity of the amino group in the 5-position. Isoxanthopterin was synthesized (75) by the condensation of 2,4,5-triamino-6-hydroxypyrimidine and mesoxalic ester in dilute acetic acid, followed by hydrolysis to give largely isoxanthopterincarboxylic acid and a small amount of xanthopterincarboxylic acid. The former decarboxylates readily on heating to 260°C. to give isoxanthopterin in excellent yield. If the condensation is carried out in 2 normal sulfuric acid, xanthopterincarboxylic acid is the principal product, possibly because the amino group in the 5-position of the pyrimidine ring is present as a salt in this medium (75). Xanthopterincarboxylic acid cannot be decarboxylated, but its easily prepared dihydro derivative is readily decarboxylated to yield dihydroxanthopterin, from which xanthopterin can be obtained by oxidation (75, 92).

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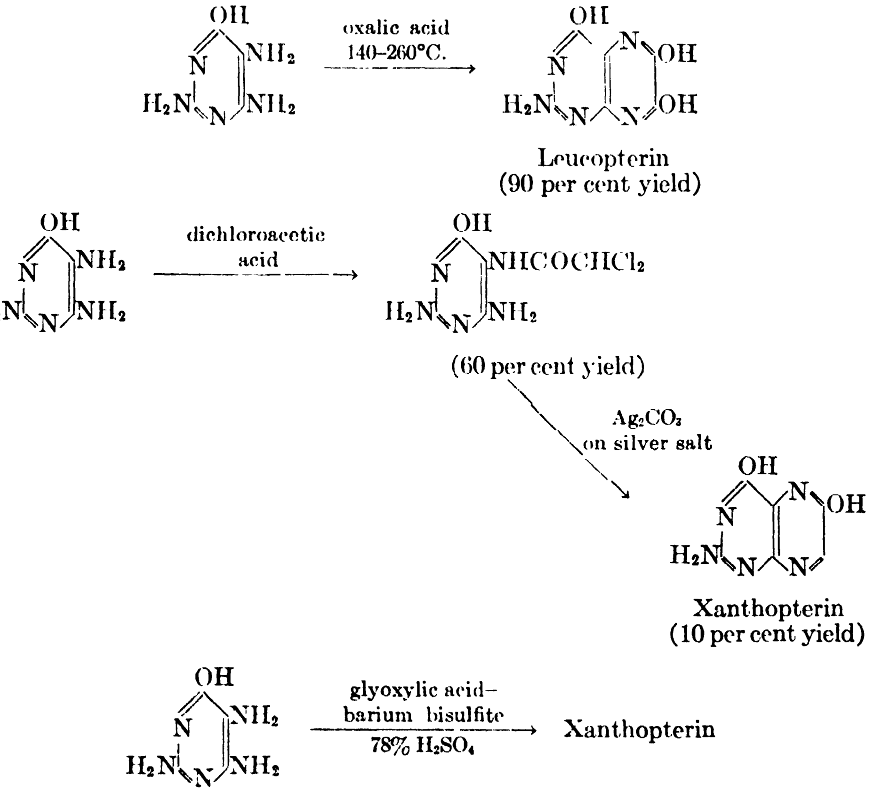
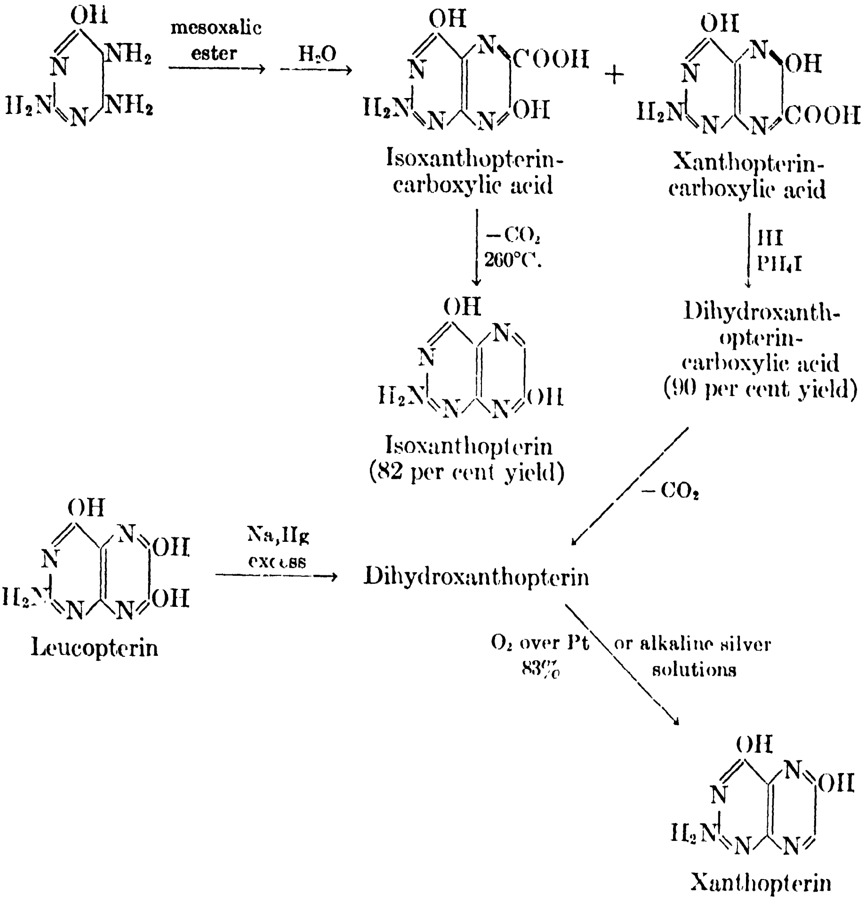
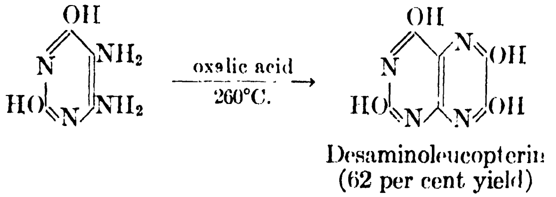
[9] It may be noted, however, that the structure of xanthopterin, and therefore of isoxanthopterin, no longer rests solely on the above assumption, since it has recently been shown (2) by means of the degradation of Weijlard, Tishler, and Erickson (100), that the methyl group in the aminohydroxymethylpteridine obtained as a degradation product of the *L. casei* fermentation factor (see page 91) is definitely at the 8-position. This methyl derivative has been oxidized to 2-amino-6-hydroxy-8-pteridinecarboxylic acid (2), which in turn has been synthesized (2) from Purrmann's isoxanthopterincarboxylic acid (75), the hydroxyl group of which must therefore occupy the 9-position. Its isomer, xanthopterincarboxylic acid, which can be converted through its dihydro compound to xanthopterin, thus carries its hydroxyl in the 8-position.

Xanthopterin has also been synthesized from 2,4,5-triamino-6-hydroxypyrimidine and glyoxylic acid–barium bisulfite by condensation in 78 per cent sulfuric acid (42), and by the reduction of synthetic leucopterin by means of an excess of sodium amalgam to give dihydroxanthopterin, which is in turn oxidized to xanthopterin by alkaline silver solutions (92). The use of 4,5-diamino-2,6-dihydroxypyrimidine and oxalic acid in Purrmann's synthesis leads to desaminoleucopterin in 62 per cent yield. All three of the well-characterized natural pterins—leucopterin, xanthopterin, and isoxanthopterin—can now be considered readily available. A summary of these synthetic methods follows:




mesoxalic ester
H_2O
Isoxanthopterin-carboxylic acid
+
Xanthopterin-carboxylic acid
$-CO_2$
260°C.
HI
PH_4I
Isoxanthopterin (82 per cent yield)
Dihydroxanthopterin-carboxylic acid (90 per cent yield)
$-CO_2$
Leucopterin
Na,Hg excess
Dihydroxanthopterin
O_2 over Pt 83%
or alkaline silver solutions
Xanthopterin

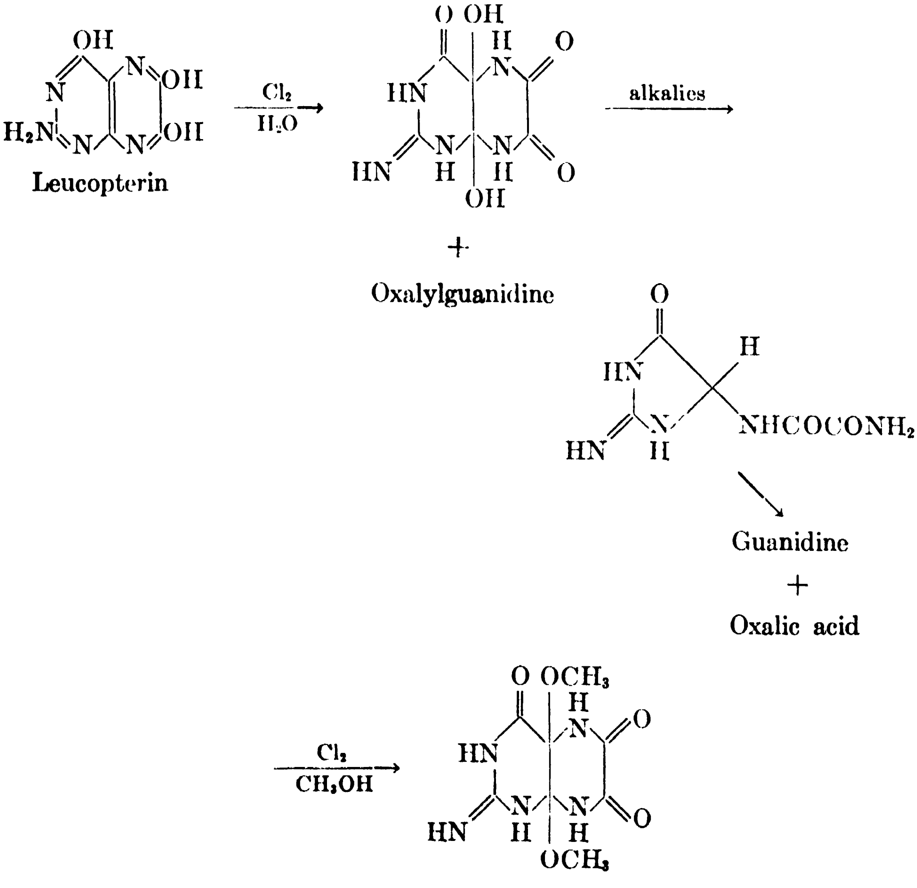


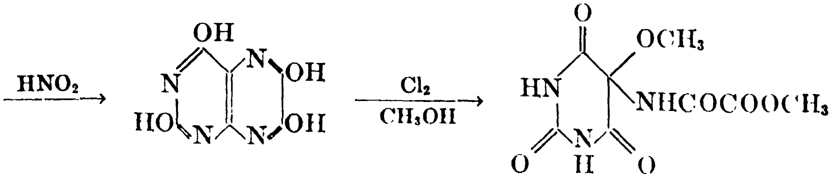
The degradative reactions leading to the recognition of the presence of a 2-aminopyrimidine ring in the pterins were for the most part carried out on leucopterin. With chlorine water it is smoothly oxidized at the ring fusion to yield leucopterin glycol, together with a small amount of oxalylguanidine, the yield of which can be increased by working at higher temperatures (102, 105). In methanol, an analogous reaction yields leucopterin glycol dimethyl ether (105). Similar oxidations of uric acid are well known. In contrast to the resistant leucopterin, which on energetic hydrolysis yields glycine, ammonia, carbon dioxide, and carbon monoxide (105), the glycol and its ether are easily hydrolyzed to yield guanidine and oxalic acid. The corresponding uric acid glycol yields urea and carbon dioxide. Careful alkaline hydrolysis of leucopterin glycol yields 2-iminohydantoinoxamide, the corresponding oxamic acid, and 2-imino-5-aminohydantoin, at first mistaken for fragments with from 13 to 15 carbon atoms (103, 107). Similar treatment of uric acid glycol yields allantoin.

The action of chlorine in methanol on desaminoleucopterin (109) yields as a principal product 5-methoxyuramil-7-oxalic acid methyl ester, which contains all of the carbon atoms of the original substance and an intact pyrimidine ring.

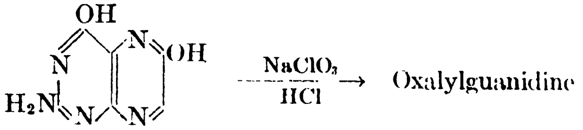
The presence of a 2-aminopyrimidine ring in xanthopterin may likewise be inferred from the fact that both it and 2,4,5-triamino-6-hydroxypyrimidine yield oxalylguanidine and oxalic acid by the action of sodium chlorate in acid solutions (85).

A résumé of these reactions (most of which are also illustrated on pages 75, 76, and 77) follows:





Desaminoleucopterin



Xanthopterin

The striking dissimilarity between xanthopterin and isoxanthopterin is manifested in a variety of ways.[10] Physically, xanthopterin is yellow and exhibits marked basic properties, whereas isoxanthopterin is colorless and only slightly basic. Great similarity in color and fluorescence exists between xanthopterin and the flavines, whereas isoxanthopterin and leucopterin show no such similarity. Unlike xanthopterin, isoxanthopterin cannot be oxidized to leucopterin by catalytically activated oxygen, but is converted to leucopterin glycol by the action of chlorine water. Finally, the difference in behavior toward fuming hydriodic acid of the dihydro compounds (see page 72) and the much greater ease of decarboxylation of isoxanthopterincarboxylic acid may be mentioned.

Erythropterin, the red pigment which accompanies xanthopterin in orange and red pierids, is much less well characterized than the foregoing compounds. The free pterin is not readily crystallizable, no crystalline salts with either acids or bases have been obtained (83), and its empirical formula is not yet known with certainty. It gives no murexide reaction, is less basic than xanthopterin, and can be separated from xanthopterin by crystallization from dilute hydrochloric acid (83).

The chromophoric system of erythropterin is highly stable to hydrosulfite (83), but reduction to a colorless leuco compound results with zinc dust and formic acid (84). Energetic acid hydrolysis yields 11–14 per cent of glycine, although its leuco compound yields 53 per cent under the same conditions (84). Its spectrum resembles that of murexide (83).

Erythropterin preparations have a tendency to give deeply colored transformation products of low solubility in ammonia (83) but there is evidence that this is not exclusively a property of erythropterin (78) and whether or not the change involves erythropterin or an impurity is not yet certain.

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[10] These differences are discussed more fully on page 72.

C. PTERORHODIN

The production of a red-violet transformation product as a result of the action of acids on crude pterins was first noted by Hopkins (32).[11] Later workers also noticed a deeply colored by-product (40, 82, 83, 107). Its formation involves oxidation of some component of crude pterins by molecular oxygen (33, 107) or by hydrogen peroxide or chlorine (78).

The substance is insoluble in water and dilute acids and in all ordinary organic solvents. It is soluble in concentrated sulfuric acid to give a brick-red solution with a violet-red tinge, and on dilution of this solution a crystalline sulfate can be isolated. Further dilution results in complete hydrolysis. It is soluble in, but slowly decomposed by, dilute alkalies (78).

The work of Schöpf (82, 83) would indicate that erythropterin, whose constitution is not yet known, may be a precursor of pterorhodin, but crystalline xanthopterin barium salt (from *Catopsilia argante*) containing no erythropterin likewise can be made to yield the pigment (107), whereas synthetic xanthopterin cannot (78). It seems clear, as Purrmann points out (78), that xanthopterin is not a precursor of pterorhodin and that a stubborn impurity, not erythropterin, in natural xanthopterin from some sources may be. Whether erythropterin is also a precursor remains undecided.

No investigation of this red-violet pigment was made until quite recently, when Hopkins (33), the original discoverer, returned to its study after a lapse of forty-seven years. He was able to outline with more precision the conditions under which pterorhodin is formed, and showed that air oxidation at pH values of 4.6 and lower of both crude erythropterin and of xanthopterin (from natural sources) purified through its barium salt, resulted in production of pterorhodin. Crude natural xanthopterin yields pterorhodin with much less ease than material purified through the barium salt, and Hopkins suggested that "native" xanthopterin probably does not yield pterorhodin, but is altered during purification. Purrmann's results (78) indicate, however, that purification of xanthopterin through the barium salt probably concentrates the tenacious impurity responsible for pterorhodin formation. Perhydrol oxidation of pterorhodin in dilute ammonia gives colorless water-soluble products, but Hopkins was unable to identify these because of lack of material.

Purrmann was able largely to clear up the question of the structure of pterorhodin in a brilliant paper published in 1944 (78). Pterorhodin is stable to alkaline hydrosulfite and to fuming hydriodic acid, but a colorless leuco compound can be prepared from it by the action of sodium amalgam. This leuco compound forms nicely crystalline salts with acids, and analyses of the perchlorate, sulfate, chloride, and iodide all agree with the formula $C_{13}H_{14}O_4N_{10}$ for the leuco compound and thus indicate $C_{13}H_{10}O_4N_{10}$ for pterorhodin, with which its analyses and those of its sulfate also agree. Pterorhodin gives oxalylguanidine in 56 per cent of the amount required for two 2-aminopyrimidine rings under conditions which yield 60 per cent from leucopterin.

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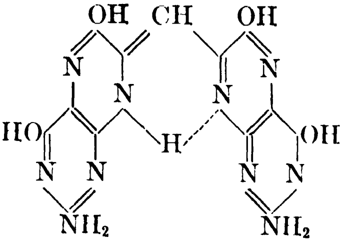
[11] Hopkins, who suggested the no longer suitable name "lepidoporphyrin" in 1895 for this substance, has recently proposed the name "rhodopterin" but Purrmann (78), after elucidation of its structure, believes "pterorhodin" is preferable, in as much as the material is not a simple pterin.

Oxidation of pterorhodin by hydrogen peroxide in concentrated sulfuric acid gave two products, leucopterin and xanthopterincarboxylic acid, which between them account for all the carbon and nitrogen atoms of pterorhodin. They were isolated by making use of the insolubility of the potassium salt of leucopterin in normal potassium carbonate, in which xanthopterincarboxylic acid is soluble.

On the basis of these observations, Purrmann proposed the accompanying structure for pterorhodin (XXXVIII), although he does not consider the structure established beyond question, since the leucopterin and xanthopterincarboxylic acid isolated did not amount to half of the pterorhodin taken, and xanthopterincarboxylic acid is converted to leucopterin, although only slowly, under the conditions of the degradation.



XXXVIII

Pterorhodin

Unlike the other pterins of known structure, the precursor of pterorhodin appears to contain more than six carbon atoms. It is similar to the known pterins in the configuration of the pyrimidine ring, is a somewhat stronger acid than xanthopterin, and is not identical with leucopterorhodin (78).

D. PHYSIOLOGICAL ASPECTS OF THE PTERINS

During the time the structural work on the pterins was being carried out, accounts pointing toward a definite physiological importance of members of this class, particularly xanthopterin, began to appear. Koschara's demonstration (40) of the occurrence of xanthopterin in human urine undoubtedly stimulated work in this direction. A suggestion that xanthopterin was in some way related to nutritional anemia was received as early as 1936, when Tschesche and Wolf (98, 99) observed that pterins, particularly xanthopterin, possessed hematopoietic activity in young rats fed an exclusive diet of goat's milk. On this diet, the animals develop an anemia reminiscent of sprue characterized by a blood picture resembling that of pernicious anemia (98). About the same time, Italian workers (55), during a chemical investigation of the antipernicious anemia factor of liver, obtained two fractions after a lengthy process of fractionation which, when combined, had appreciable action against pernicious anemia. One of these fractions was thought to contain a pterin, the other a nucleotide and a polypeptide.

In 1939 Koschara observed an increase in urinary secretion of xanthopterin during a variety of disorders of the hematopoietic system (as well as in some other pathological conditions) (46). The distribution of xanthopterin in many tissues in both well and diseased men has been studied by this author (45, 46) who, because of the parallelism in occurrence between riboflavin and xanthopterin, has suggested that these two pigments may act as a functional unit (45).

A further indication of the relationship between the pterins and hematopoiesis appears in the work of Jacobson, who has shown not only that xanthopterin and leucopterin evoke a reticulocyte response in splenectomized rabbits (38), but also that the argentaffine cells of stomach and intestinal epithelium, whose location agrees with that of the substance active against pernicious anemia, contain a pterin (37) the intensity of whose fluorescence spectrum parallels hematopoietic activity (39).

Xanthopterin is also hematopoietically active in anemic fingerling salmon (59, 89).

Two independent observations indicate that yeast, whose content of preformed folic acid is low, and liver, grass, and urine, when incubated with fresh liver, produce folic acid (94, 114) and that these materials therefore contain a precursor of folic acid. The stability to heat and the adsorption-elution characteristics of this precursor are similar to those of xanthopterin (114). Synthetic xanthopterin, but not leucopterin, shows the effect.

In spite of the association of xanthopterin with nutritional anemia which is evident from the foregoing, a great deal of evidence exists indicating that while xanthopterin may possess hematopoietic activity, it alone is not sufficient to bring about remission of these anemias in all species. Thus it has been shown that rapid regeneration of a normal blood picture in dogs rendered anemic by phlebotomy occurs when dry or whole liver is added to a whole milk diet, but that the liver can not be wholly replaced by, among other things, xanthopterin (57). Likewise, while xanthopterin delays the development of nutritional anemia in monkeys and produces a hematopoietic response in anemic animals, it does not offer full protection against vitamin M deficiency (see page 89) (93, 96) nor can it replace vitamin B_c in the diet of the chick (60). Furthermore, whereas xanthopterin appears to produce an immediate gain in weight and a pronounced leucocyte response in rats rendered leucopenic by succinylsulfathiazole (93; see also, however, 114), distribution of the white cells may not be normal after this therapy (93).

In addition to the association of xanthopterin with hematopoiesis, there are other indications that this class of compounds is of physiological importance. Polanovski and his coworkers have shown that a number of pteridine derivatives of rather divergent structures possess vitamin B_1 activity of a low order in rats and pigeons but not in the flagellate *Polytomella caeca*. Fluorescyanine, a pigment possibly related to the pterins, which has been isolated by these workers from carp scales has a similar but stronger action (8, 9, 10, 11, 12, 67).

Xanthopterin and especially folic acid also appear to possess a growth-inhibiting effect on malignant tumors in mice (26, 54).

The results of a pharmacological investigation of xanthopterin have been published by Hörlein (27).

VI. Folic Acid[12]

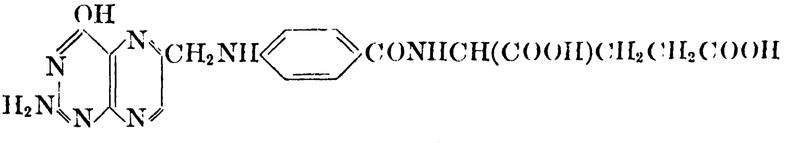
A. DIETARY FACTORS RELATED TO FOLIC ACID AND THEIR INTERRELATIONSHIPS

The discovery of folic acid, one of the most recently recognized members of the vitamin B complex, was the result of nutritional work, both bacterial and animal, in several laboratories. Widely divergent approaches were used and the various lines of experimentation converged only at a relatively late stage in the investigations. No detailed account of the physiological work, which is treated thoroughly in the review of Berry and Spies (5), can be given here. It will be sufficient to say that two well-studied dietary factors for animals, i.e., "vitamin M," without which monkeys develop a fatal blood disorder characterized by leucopenia and sometimes anemia (53), and "vitamin B_c," lack of which results in poor growth and macrocytic hyperchromic anemia in chicks (28), and several growth factors for the bacteria *Lactobacillus casei* and *Streptococcus lactis* R (for a complete bibliography see reference 5) variously known as "norite eluate factor," "folic acid," "*L. casei* factor," "SLR factor," etc., are considered to be, if not identical, very closely related, and the name "folic acid" appears now to be applied indiscriminately to various members of the group. Crystalline substances corresponding to four of the above have been isolated, i.e., vitamin B_c from both liver and yeast (6, 63), vitamin B_c conjugate from yeast (64), and two *L. casei factors*, one from fermentation products and one from liver (35, 90).

B. THE *L. casei* LIVER FACTOR

1. *Identity and physiological aspects*

The *L. casei* factor from liver has been shown to be identical with vitamin B_c (65), and its structure (XXXIX) has been established by degradation and synthesis (1, 2).



XXXIX

The other two crystalline substances, the *L. casei* fermentation factor and vitamin B_c conjugate, are peptide conjugates of this simpler molecule, which has been called "pteroylglutamic acid," and yield on hydrolysis two and six additional molecules of *l*(+)-glutamic acid, respectively. Pteroylglutamic acid is now commercially available, and its therapeutic value in various clinical types of macrocytic anemia and sprue has been clearly established (5, 15). The clinical evidence for its hematopoietic activity has been reviewed by Berry and Spies (5). It also has been shown to be active in nutritional anemias of monkeys (112; see also 16), giving the typical vitamin M response, and corrects or prevents the blood disorders produced in rats by succinylsulfathiazole (20) or thiourea and thyroxine

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[12] An excellent review covering the nutritional and physiological aspects of the folic acid problem and the therapeutic applications of the *Lactobacillus casei* liver factor has recently been published by Berry and Spies (5).

(14). Both pteroylglutamic acid and the *L. casei* fermentation factors are active in the chick, possibly equally so on a molar basis (34), and it appears likely that pteroylglutamic acid (XXXIX) or various peptide conjugates of it with *l*(+)-glutamic acid are involved in all of the physiological effects mentioned above.

The occurrence of *p*-aminobenzoic acid, long a recognized member of the vitamin B complex, in combined form in "folic acid" is of great biochemical interest. It has been shown that the synthesis of pteroylglutamic acid from *p*-aminobenzoic acid is the site of sulfonamide inhibition in the organism *S. fecales* R (51). *p*-Aminobenzoic acid may be utilized in other ways than in the formation of pteroylglutamic acid, however, since the latter substance has less than 0.001 per cent of the activity of *p*-aminobenzoic acid for a mutant strain of *Escherichia coli* (52).

Folic acid concentrates have been reported to have tumor-inhibiting activity against malignant mouse tumors, chiefly mammary adenocarcinomas (26).

2. *Degradation and synthesis*

The elucidation of the structure[13] of the *L. casei* liver factor affords a splendid example of the application of information obtained in what might be regarded as a remote and possibly academic field, that of the pterins, to the solution of a problem of great importance for practical therapy. The timely completion of the structural work on the pterins in 1940 and 1941 provided the necessary knowledge for the rapid solution of the problem of structure and synthesis of the *L. casei* liver factor which must otherwise have been greatly delayed. A résumé of the degradative work follows (2):

The close relationship between the *L. casei* fermentation factor and the *L. casei* liver factor was established (2) by anaerobic alkaline hydrolysis by which the fermentation factor is converted into the *dl* liver factor (pteroylglutamic acid) with the simultaneous formation of 2 moles of glutamic acid. Similarly, enzymatic hydrolysis of vitamin B_c conjugate yields pteroylglutamic acid (64) and 6 moles of *l*(+)-glutamic acid are liberated by acid hydrolysis (65). Aerobic alkaline hydrolysis of the *L. casei* fermentation factor yields two fractions in equimolar amounts, one of which is a highly fluorescent dibasic acid (pK_a values 3.9 and 7.7) whose fluorescent behavior, ultraviolet-light absorption, and ultimate analysis coupled with the isolation of guanidine following oxidation with chlorine water and acid hydrolysis suggested for its structure a 2-aminopteridine nucleus carrying a hydroxyl and a carboxyl group. It was fully identified as 2-amino-6-hydroxy-8-pteridinecarboxylic acid (XL) by comparison with an authentic sample prepared from isoxanthopterincarboxylic acid (XLI) by chlorination with phosphorus pentachloride, followed by reduction with hydriodic acid. It can be decarboxylated at 300°C. to a monobasic acid, pK_a 8.0, which is identical with synthetic 2-amino-6-hydroxypteridine (XLII) prepared from 2,4,5-triamino-6-hydroxypyrimidine and glyoxal. The hydroxyl in the 9-position of isoxanthopterincarboxylic acid is thus the one removed in the chlorination and reduction described above.

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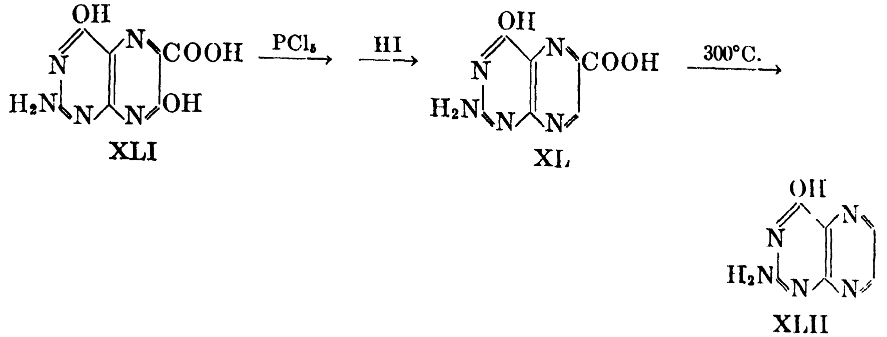
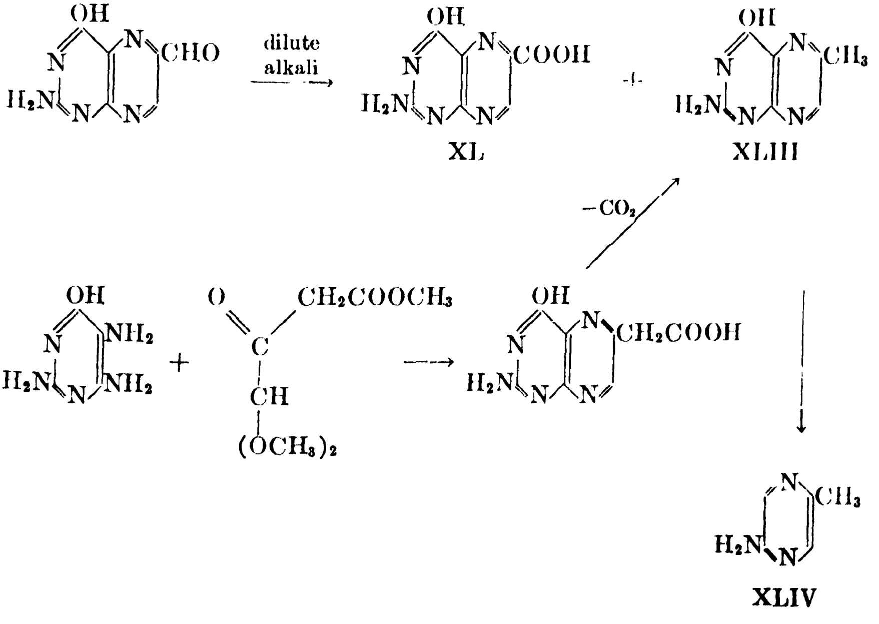
[13] **Although the synthesis of the material was announced in August, 1945 (1), neither the structure nor the details of degradation and synthesis were disclosed for nearly a year (2).**



XLI XL XLII

The second fraction from aerobic alkaline hydrolysis showed the presence of an aromatic amino group and yielded *p*-aminobenzoic acid after acid hydrolysis.

A second cleavage of the *L. casei* fermentation factor was achieved with the aid of sulfurous acid, and again yielded a pteridine fraction and an aromatic amine fraction. In this case, however, the pteridine fraction reacted readily with aldehyde reagents and on standing in dilute alkali in the absence of air underwent a dismutation to yield the carboxylic acid described above and 2-amino-6-hydroxy-8-methylpteridine (XLIII), identified by comparison with a sample synthesized by the condensation of 2,4,5-triamino-6-hydroxypyrimidine and methyl γ,γ-dimethoxyacetoacetate, followed by decarboxylation of the 2-amino-6-hydroxy-8-pteridineacetic acid so obtained. The methyl compound and the corresponding acetic acid can both be oxidized to the previously described 2-amino-6-hydroxy-8-pteridinecarboxylic acid (XL) by hot alkaline

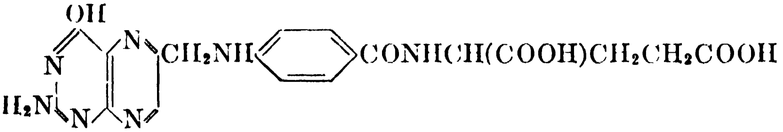


XL XLIII XLIV

permanganate. Degradation of the methyl compound by the method[14] of Weijlard, Tishler, and Erickson (100) gave 2-amino-5-methylpyrazine (XLIV), confirming the position of the methyl group.

Acid hydrolysis of the aromatic amine fraction liberated three-fourths of the nitrogen as α-amino acid nitrogen, and again p-aminobenzoic acid was isolated. The presence of 3 moles of glutamic acid in the hydrolysate was indicated by microbiological assay. Aqueous hydrolysates of the *L. casei* fermentation factor had yielded pyrrolidonecarboxylic acid, a further indication of the presence of glutamic acid.

The necessity for oxygen in the alkaline cleavage, and the simultaneous liberation of an aromatic amino group and the pteridinecarboxylic acid in this reaction, suggests the linkage of the pteridine nucleus to the amino group through a methylene group; accordingly structure XXXIX was proposed for the *L. casei* liver factor.



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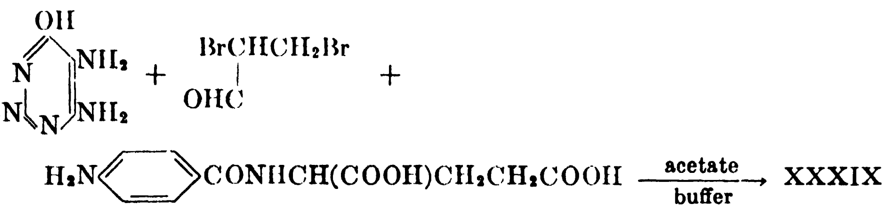
This structure was confirmed by two syntheses, both of which gave material identical in physical and physiological properties with the natural material (1, 2). The first synthesis was achieved by condensing equivalent amounts of 2,4,5-triamino-6-hydroxypyrimidine, α,β-dibromopropionaldehyde, and p-aminobenzoyl-$l(+)$-glutamic acid in an acetate buffer. The condensation proceeds by way of an intermediate dihydro compound which is oxidized during the course of the reaction, and yields 15 per cent of active material as determined by microbiological assay. A lengthy purification process affords the pure crystalline *L. casei* liver factor in unspecified yield.



A second synthesis utilized the interaction in the presence of potassium iodide of 2,4,5-triamino-6-hydroxypyrimidine with the condensation product of pyridine and α,β-dibromopropionaldehyde to give N-[(2-amino-6-hydroxy-8-pteridyl)-methyl]pyridinium iodide (XLV), which was then condensed with p-aminobenzoyl-$l(+)$-glutamic acid by means of sodium methoxide in ethylene glycol at 140°C. The crude product again contained about 15 per cent of biologically active material, from which the crystalline product could be isolated by the same purification process.

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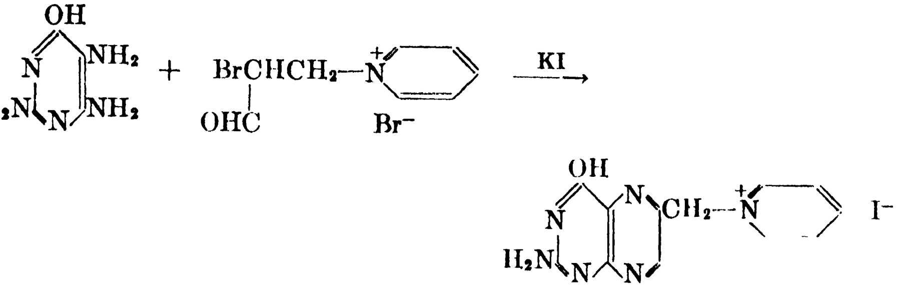
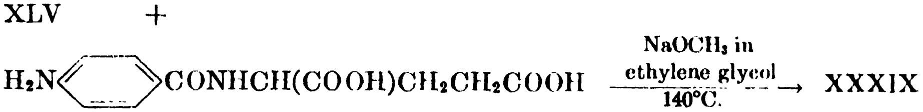
[14] Angier *et al.* (2) do not state which of the two methods described by these authors was used in the degradation.



XLV



That the pyridinium methyl group in the preliminary condensation product occupies the 8-position was shown by alkaline permanganate oxidation to 2-amino-6-hydroxy-8-pteridinecarboxylic acid (XL).

The same synthetic methods were used to prepare *N*-[(2-amino-6-hydroxy-8-pteridyl)methyl]-*p*-aminobenzoic acid ("pteroic acid"), which proved active for *S. fecalis* R but inactive for *L. casei* and for the chick (2).

Note added in proof: A publication describing in considerable detail the characterization of vitamin B_c and its isolation as the free acid and as its methyl ester from hog liver, horse liver, and from yeast has recently appeared (64a). Publications describing its degradation are in press.

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THE PRESENT STATE OF ORGANOSILICON CHEMISTRY[1]

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[1] When the first two authors, who were at work on a review on this subject, learned that the latter two were also writing a review on the same subject based on a thesis submitted by James Hartt in 1941 in partial fulfillment of the requirements for a degree of Master of Arts in Western Reserve University, they suggested that efforts be combined. The last three authors gratefully acknowledge the heavy burden carried by the first named author in integrating this information. E. G. R., H. S. B., J. H.

McBee "Keysort" punch cards were used in the assembly of this paper.

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I. INTRODUCTION

Nature provides no ready source of organosilicon compounds,[3] for while silicon is abundant in the earth, it occurs in the highly oxidized form. If organosilicon compounds have any utility, then, it could not have been apparent to the pioneer investigators; only curiosity could have led them to find out how to make such compounds and then to study their behavior. For this reason organosilicon chemistry was and is purely a product of laboratory research. Progress in the field has followed closely the improvements in methods of synthesis, and has moved ahead in several well-defined surges originating in the development of new methods. Now that the commercial manufacture and application of organosilicon materials (49, 290) have brought wider interest in the field and have encouraged many new investigations, it has seemed appropriate to review the present state of our knowledge of organosilicon compounds.

As seen by the authors, the chief function of such a review paper at this time is to assemble a complete bibliography and to comment upon the individual publications to an extent that will make the list more valuable and more usable to the research chemist. The bibliography at the end of this paper is believed to be complete to June 3, 1946, insofar as the facilities at the disposal of the authors made that possible. In the preparation of the bibliography it has seemed advisable to define organosilicon compounds as those in which there is at least one carbon–silicon bond (306), i.e., those in which one or more carbon atoms are linked directly to silicon atoms. The articles have been selected in accordance with this definition; hence articles on the organic esters of orthosilicic acid or any other class of compounds in which organic groups are linked through some third element to silicon atoms have not been included.

A further aim of the authors has been to collect data on the physical constants of all the known organosilicon compounds, so that the data would be available for ready reference. Tables of these compounds and their physical properties therefore also appear at appropriate places in the paper, and it is believed that these are complete through the publication date.

With the tables and bibliography appearing in this form there is much less need for detailed abstracting of the separate publications, and therefore it has been the intention of the authors to discuss classes of compounds and types of reaction rather than to paraphrase the findings of the individual investigators.

Other reviews of the literature have been presented by Kipping (168), Krause and von Grosse (196), Bygdén (41), and Dolgov (65).

II. NOMENCLATURE

The early practice of naming organosilicon compounds after their organic analogs was soon found to be cumbersome and ambiguous (306); nevertheless some of the oldest terms have persisted up to the present time. Every investigator in the field has felt the need for a satisfactory and accepted terminology to simplify the problem of identifying compounds, but conflicting views have long prevented the adoption of one scheme. The first consistent system of nomenclature was devised by Kipping (147, 155, 158), who based the names of all his compounds on the name *silicane* for the parent substance SiH_4. The Kipping system was unambiguous, but its use often resulted in unpronounceable names of fifteen or more syllables. It is not surprising, then, to find the more recent trend toward the shorter names based upon the system devised by Stock (342, 344) for naming the normal hydrides of silicon (306). According to this system the parent substance SiH_4 is called *silane*, a hydroxy derivative is called *silanol*, a compound with alternate silicon and oxygen atoms is a *siloxane*, etc. The organic compounds are then named as derivatives of the hydrides. The matter is no longer one for controversy, because it has been resolved by a committee on nomenclature of the American Chemical Society, and the recommendations of that committee are followed in this paper (50). The committee has established the root name of *silane* for SiH_4, and the names of the simpler types of compounds become *siloxane*, *silazane*, *cyclosiloxane*, *cyclosilazane*, *silanol*, etc. Groups are named as derivatives of the hydride groups such as silyl (H_3Si—), silylene (H_2Si=), disilanyl ($H_3Si—SiH_2$—), siloxy (H_3SiO—), etc. It is hoped that all authors in the field will adopt and encourage the American Chemical Society system, so that in the future those who abstract articles or assemble bibliographies will find their tasks less difficult.

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[3] The presence of silicon dioxide in the ash obtained by burning straw or feathers indicates the presence of soluble or dispersed compounds of silicon in the living tissue, but the state of combination has not been clearly defined and it seems unlikely that organosilicon compounds (with the definition used herein) are present (68).

III. METHODS FOR THE SYNTHESIS OF ORGANOSILICON COMPOUNDS

As was pointed out in the introduction, investigations of organosilicon compounds have followed quite closely patterns set by the available methods of synthesis. It seems appropriate to consider these individual methods before going on to a discussion of the various classes of compounds. It will then be seen that the separate compounds fall into groups or classes for which general methods of preparation may be given.

A. SYNTHESIS OF ORGANOSILANES AND ORGANOCHLOROSILANES

We may classify the available methods of synthesis as either substitution methods or direct methods (290a). In the substitution methods some reactive covalent compound of silicon (such as a halide or ester) is employed as a starting material, and the desired organic groups are attached to the central silicon atom by a reaction which involves substitution for the halogen or ester groups. In the direct method, crystalline or elementary silicon is caused to react directly with a hydrocarbon halide to produce a mixture of organosilicon halides. The substitution methods have been in use a great deal longer than the direct method, but both find their spheres of application in the plant as well as in the laboratory.

Most of the substitution methods involve the reaction of an active organometallic compound with a silicon halide or ester, and therefore require the preliminary preparation of that active compound. Thus the method of Friedel and Crafts (81, 85) involves the reaction of zinc alkyls or aryls with silicon tetrachloride or with ethyl orthosilicate according to the metathesis:

$$2ZnR_2 + SiX_4 = SiR_4 + 2ZnX_2$$

The substitution is stepwise and hence may be used for the attachment of one to four organic groups, depending upon the molar proportions and the reaction conditions used. Such reactions are carried out in sealed tubes at a temperature of 150–200°C. or more, so that the quantity which can be prepared in one operation is necessarily limited. Moreover, the preparation of the necessary zinc alkyls is in itself an arduous task, and these highly poisonous metal alkyls are unpleasant substances to handle in the laboratory. Nevertheless the reaction still finds application in some exceptional circumstances.

In 1884 Pape (258) introduced a variation in which a mixture of propyl iodide, metallic zinc, and silicon tetrachloride was heated in a sealed tube instead of preparing the zinc alkyl separately, but this method has not been widely used.

Another variation which was used a great deal by Ladenburg eliminated the sealed tube by the use of metallic sodium along with the zinc alkyl (203):

$$2Na + Zn(C_2H_5)_2 + Si(OC_2H_5)_4 = (C_2H_5)_2Si(OC_2H_5)_2 + 2NaOC_2H_5 + Zn$$

In an elaboration of the mechanism for this reaction, Ladenburg was able to show that the alkyl groups which were attached directly to silicon were derived from the zinc alkyl rather than by reduction of the ester groups on the silicon; therefore it seems probable that the real alkylating agent was a sodium alkyl derived from reaction of the metallic sodium in the zinc alkyl. The higher reactivity of the sodium alkyl makes unnecessary the higher temperatures for which a sealed tube is required.

Alkylation of chlorosilanes in the gas phase rather than in solvents or in sealed tubes was accomplished by Stock (347) in his investigation on the silicon hydrides. He found that the vapor of dimethylzinc would react with the gaseous chlorosilanes at moderate temperatures to deposit zinc chloride and accomplish a stepwise substitution of methyl for chlorine on the silicon. A different kind of vapor-phase alkylation (116) involves passing the mixed vapors of a silicon halide and alkyl halide over a finely divided reactive metal and abstracting the chlorine as metal chloride, yielding a mixture of organosilanes. In this latter method it is possible that an alkyl of the reactive metal is formed first and that this alkyl then reacts at once with the silicon tetrachloride, but it is not necessary that this intermediate reaction be assumed.

The second method to come into general use in the period following 1884 involved the condensation of silicon tetrachloride and an alkyl or aryl chloride with metallic sodium (258). This reaction usually is carried out in dry ether as a solvent, and it is customary to add a little ethyl acetate as catalyst (178). With an excess of the alkyl or aryl chloride, tetrasubstitution takes place:

$$SiCl_4 + 4RCl + 8Na = SiR_4 + 8NaCl$$

The reaction is highly exothermic, the liberated energy being sufficient to break silicon–silicon bonds (318). For this reason the method cannot be used for preparing organic derivatives of disilanes or siloxanes, nor can it be used satisfactorily for preparing mono- and di-substituted chlorosilanes. In order properly to control the substitution reaction it is necessary that the heat of the sodium reaction be dissipated in some way. One way of accomplishing this is to carry out the synthesis in two stages (320). For example, metallic sodium reacts with monochlorobenzene in dry ether to produce reactive phenylsodium, and then the solution or suspension of phenylsodium is introduced in proper proportion into a solution of silicon tetrachloride. The second reaction then can be controlled to give satisfactory yields of the intermediate substitution products like dichlorodiphenylsilane. Carried out in this way, the sodium condensation method is about as convenient as the Grignard method.

The application of the Grignard reagent to organosilicon chemistry was first accomplished independently by Kipping (146) and Dilthey (63), but Kipping made by far the most extended use of the method. As ordinarily carried out, the Grignard reagent is prepared in a normal manner and then added to a stirred solution of silicon tetrachloride in ether. Should the Grignard reagent have a very low reactivity, however, it may be separated from the ether in which it was prepared and heated with the silicon tetrachloride in a sealed tube, or in a high-boiling solvent (52, 319). Several simplifications have been suggested, among them the introduction of a mixture of silicon tetrachloride and alkyl chloride to a suspension of magnesium turnings in ether, or the addition of magnesium to a solution of the mixed halides. The use of alcohol-free and very dry ether as a solvent for the Grignard reaction has been avoided in some cases by carrying out the reaction in an excess of one of the reagents. Thus, monochlorobenzene reacts with magnesium in an excess of the chlorobenzene as solvent (290a), and ethyl orthosilicate serves as solvent for the preparation of a Grignard reagent and for the reaction of that reagent with the ethyl silicate (5, 6, 8, 9, 10). In the latter instance the method becomes a one-stage reaction in which the organic halide, ethyl silicate, and magnesium are heated in a sealed vessel under pressure (234).

Substitution of the chlorine in silicon tetrachloride by Grignard reagents takes place as a series of consecutive competitive reactions, to produce a mixture of products in which the individual compounds are present in proportions depending upon the relative concentrations of the reagents and a relative reactivity of the chlorine atoms on each compound (95b). The mathematical expression for the proportion of products agrees with the experimental yield data only when a high reactivity is assigned to $RSiCl_3$. It seems that the chlorine atoms attached to silicon are not uniformly reactive nor reactive in proportion to their number, but rather achieve a characteristic reactivity which is dependent upon the symmetry of the molecule and the kind of substituents already present.

Another substitution method which is related to the Grignard synthesis makes use of the reaction between alkyls of lithium and a chlorosilane (76, 102a). The lithium alkyl is prepared and handled much like a Grignard reagent, but is more reactive and so is particularly suited to syntheses in which the Grignard reagent provides only meager yields. There is also a related reaction between lithium alkyls and silicon-hydrogen bonds (103a, 246a). This has been used to prepare butyltriethylsilane from triethylsilane and butyllithium in ether solution:

$$(C_2H_5)_3SiH + n\text{-}C_4H_9Li \rightarrow (C_2H_5)_3(n\text{-}C_4H_9)Si + LiH$$

Ethyl ether seems to be necessary for this reaction, for it is not found to occur in petroleum ether or in tertiary butyl alcohol. Lithium amide and lithium ethoxide react similarly with triethylsilane in ammonia or ethyl alcohol, respectively, but in these syntheses the lithium hydride reacts with the solvent to regenerate the amide or ethoxide and release hydrogen.

A radically different substitution method involves the absorption of ethylene or of other olefinic hydrocarbons in silicon tetrachloride at elevated temperature and under high pressure (325):

$$CH_2{=}CH_2 + SiCl_4 = ClC_2H_4SiCl_3$$

This reaction has been reported to take place at 10–100 atm. and in the presence of molar proportions of a catalyst such as aluminum chloride or oxychlorides of mercury or copper. Substitution of only one chlorine on the silicon is indicated in the only published report (325). The reaction of acetylene with silicon tetrachloride under similar conditions is stated to produce β-chlorovinyltrichlorosilane, and the reaction of carbon monoxide is said to produce trichlorosilylcarbonyl chloride. All of these products have reactive chlorine atoms in the organic portions and therefore should prove to be interesting intermediates for further organosilicon syntheses.

A related reaction is described in which saturated hydrocarbons react with silicon tetrachloride in the vapor phase at a temperature of 450°C. or more to produce a mixture of organosilicon halides (250). In this and the preceding method no reactive metal is used as condensing agent, but the methods still involve substitution of chlorine in the silicon tetrachloride and so may be classed as substitution reactions.

The direct synthesis (289, 290a, 299) brings about simultaneous reaction of organic groups and halogen atoms with elementary silicon to produce organosilicon halides:

$$2RCl + Si = R_2SiCl_2$$

$$4RCl + 2Si = R_3SiCl + RSiCl_3 \text{ etc.}$$

This is a general reaction for alkyl and aryl halides in either the liquid or the vapor phase. However, it is most convenient to use alkyl or aryl chlorides as starting material and to carry out the reaction in the gas phase at a temperature of 200–450°C., depending upon the reactivity of the particular chloride (302). It is apparent that at the higher temperatures which may be required for reaction of the more inert chlorides the organic compounds may suffer considerable pyrolysis, with consequent deposition of carbon in the reactive zone. Such decomposition can be avoided in large part by the use of a metallic (289) or metal oxide (303) catalyst which will reduce the temperature required for effective reaction. Powdered copper is such a catalyst, and has been used satisfactorily in the reaction of methyl chloride with elementary silicon to prepare methylchlorosilanes. The use of copper enables one to reduce the reaction temperature by about 100°C. and so to obtain satisfactory conversion of the methyl chloride without large losses by pyrolysis.

The action of the catalyst in the direct reaction is of interest as well as of economic importance, and therefore has been studied in some detail (118). It appears that the methyl chloride first reacts with finely divided copper to produce cuprous chloride and methylcopper, and that the latter then decomposes quite rapidly into free copper and free methyl groups. The cuprous chloride is readily reduced by silicon at the temperature of the reaction, regenerating free copper and transferring the chlorine to the silicon. The partially chlorinated silicon then is able to take up free methyl groups or more chlorine atoms until it has four substituents, whereupon it becomes sufficiently volatile to leave the reaction zone. This reaction mechanism would add methyl groups and chlorine atoms at random, so that a mixture of all possible methyl- and chlorine-substituted silanes becomes possible. It is found that silicon tetrachloride, tetramethylsilane, and all the intermediate methylchlorosilanes are produced. If the copper catalyst is not sufficiently effective or the temperature rises to too high a value, methyl groups are lost by pyrolysis and the product becomes richer in chlorine. The copper therefore is classed more properly as a chemical reagent than as a physical catalyst, but because of the cyclic reactions it is used over and over without leaving the scene of the reaction. It is interesting to note that in the reaction of chlorobenzene with silicon to form dichlorodiphenylsilane as the principal product, finely divided silver is more effective than copper as a catalyst (302).

Of the five general methods which have been described, the Grignard method seems most universally applicable. Of the others, the sodium condensation method has been used principally to prepare tetrasubstituted silanes, and the direct method has been used principally to prepare dialkyl- or diaryl-substituted dichlorosilanes.

B. SYNTHESIS OF ORGANOFLUOROSILANES

1. By the Grignard reaction

The reaction of the Grignard reagent with silicon tetrafluoride is carried out in the same manner as with the other silicon halides, but with considerably different results. No mono- or di-substituted products have been reported, the main product in all cases being R_3SiF with smaller amounts of the SiR_4 compound (100, 135, 247, 248).

When silicon tetrafluoride was passed into ethyl-, propyl-, butyl-, or amylmagnesium chloride, the reaction was complete in an hour, yielding mostly the trialkylfluorosilanes (100). With the ethylmagnesium bromide, some tetraethylsilane was formed.

While (248) it is reported that tetraphenylsilane cannot be prepared from silicon tetrafluoride even with excess of the Grignard reagent, others have usually obtained some tetrasubstituted product.

'Good yields of tribenzylfluorosilane with some tetrabenzylsilane using silicon tetrafluoride at room temperature have been reported (247). The silicon tetrafluoride (333) has also been introduced into the reaction in the form of sodium fluosilicate, and it has been found that there is no appreciable formation of tetrabenzylsilane until a temperature of 160–170°C. has been reached. By using five times the theoretical amount of sodium fluosilicate, the yield was increased from 20 per cent fo 54 per cent (334).

2. From silicones

Triethylfluorosilane (77) has been prepared by treating a mixture of hexaethyldisiloxane ($(C_2H_5)_6Si_2O$) and concentrated sulfuric acid with sodium or ammonium fluoride. After standing for some hours the mixture was extracted with petroleum ether, from which it was separated by distillation. Yields were reported to be quantitative.

Diethyldifluorosilane (73) has been made by gently warming a solution of diethyl silicone dissolved in concentrated sulfuric acid to which calcium fluoride had been added, whereupon a reaction set in forming a layer of a clear liquid on the surface, which on distillation proved to be diethyldifluorosilane.

Ethyltrifluorosilane (73) has been prepared by distilling a mixture of ethylsilanetriol, calcium fluoride, and sulfuric acid.

By bubbling anhydrous hydrogen fluoride through a mixture of a methyl silicone oil, sulfuric acid, 30 per cent fuming sulfuric acid, and Tergitol (wetting agent), and passing the effluent gas through absorbent sodium fluoride pellets to remove excess hydrogen fluoride, a condensate was obtained which upon distillation yielded pure trifluoromethylsilane, difluorodimethylsilane, and fluorotrimethylsilane (24a).

The reaction of anhydrous hydrogen fluoride, or mixtures which yield it, in the presence of a suitable reagent to absorb the water produced by the reaction, upon silicones yields fluorides corresponding to the organochlorosilanes from which the silicone was originally made and appears to be a general reaction.

3. From organochlorosilanes

Various fluorides with or without catalysts react with organochlorosilanes to yield organofluorosilanes.

The fluorides of lead (73), zinc (73, 252a), antimony (24b–24g), and calcium (24d) have been used. Lead fluoride reacts sluggishly and antimony fluoride rapidly, while zinc fluoride is intermediate in speed.

The three methyl- (252a) and ethyl-fluorosilanes (73), trifluorophenylsilane (73), and difluorodiphenylsilane (73) have been prepared by the reaction of zinc fluoride on the corresponding chloride. No evidence of the formation of fluorochlorides was obtained.

Organochlorosilanes are not only solvolyzed by water and liquid ammonia, but also by anhydrous hydrogen fluoride (268). When the alkylchlorosilanes are added to anhydrous hydrogen fluoride, hydrogen chloride is evolved. After standing for some hours, the residual hydrogen fluoride is removed by the addition of anhydrous sodium fluoride, and the alkylfluorosilane is purified by distillation.

C. SYNTHESIS OF ORGANOCHLOROFLUOROSILANES

By the reaction of sublimed antimony trifluoride in the presence of about 5 per cent of antimony pentachloride as a catalyst, chlorine attached to the

silicon atom in an organochlorosilane may be replaced with fluorine stepwise (24b). The yields of the chlorofluorides are low compared to the completely fluorinated product. The replacement of one chlorine atom by a fluorine atom not only lowers the boiling point about 35°C., but also lowers the threshold fluorinating temperature to a considerable extent, with the result that the fluorination is greatly accelerated. In the fluorination of an organotrichlorosilane, it is difficult to obtain more than traces of the monochlorodifluoro compound by the usual reaction procedure, but the completely fluorinated product is obtained in abundance (24c, 24d, 24e). The yield of chlorofluorides can be increased by forcing the reaction as rapidly as possible, with no condensation of partially fluorinated products and with rapid removal of all gaseous products (24f, 24g).

Equal amounts of all three fluorination products of trichloromethylsilane have been obtained by passing the vapors of trichloromethylsilane over calcium fluoride powder heated to 200°C. at 700–750 mm. pressure in a rotating copper tube, although the total yield was small (24d).

IV. BEHAVIOR OF CLASSES OF ORGANOSILICON COMPOUNDS

A. NORMAL ALKYLS OF THE TYPE SiR_4, R_3SiSiR_3, ETC.

Compounds of the type SiR_4, in which all of the organic radicals (R) are alkyl or aryl hydrocarbon groups, are the most stable substances known to organosilicon chemistry. Tetraethyl- and tetramethyl-silanes are inert to alkalies and to concentrated sulfuric acid and are affected only by strong oxidizing agents. The thermostability of tetraphenylsilane and its resistance to oxidation have been commented upon at length (196), and it must be conceded that the substance is far more stable toward reagents and toward pyrolysis than are most hydrocarbons. The phenyl groups resist oxidation at the boiling point (*ca.* 450°C.), and pyrolysis of the phenyl groups sets in at some much higher (but as yet undetermined) temperature. It would be a great mistake, however, to conclude that carbon–silicon bonds in general are similarly inert or convey exceptional stability to the rest of the molecule. In molecules with very high organic content the effect of a silicon atom is greatly diluted or is entirely lost. More than this, the introduction of a silicon atom may even introduce a point of molecular instability, as is found in the ready hydrolysis of ethylphenylsilanes (355). A wide variation in chemical behavior therefore is encountered in the normal alkyls and their derivatives.

Alkyls of the type SiR_4 may be prepared by the Wurtz reaction, by the Grignard synthesis, or by the reaction of zinc, lithium, or mercury alkyls with silicon tetrachloride. It has been found that mercury diaryls are more satisfactory for preparing aryl derivatives of silicon than are the corresponding zinc compounds, while the reverse is true for the aliphatic derivatives.

Besides the alkyls in which all four groups are identical there is a long series of related alkyls containing two, three, or four different alkyl or aryl radicals. These are almost always prepared by the successive reaction of different Grignard reagents upon silicon tetrachloride, and they show reactions that are characteristic of all the constituent groups. There appears to be no steric hindrance to the attachment of very large groups; the silicon atom has a sufficiently higher atomic volume than carbon so that four tolyl or naphthyl groups may be attached. The physical constants of these and the other known normal alkyls of the type SiR_4, together with references to the original papers describing their preparation, are given in table 1.[4]

Higher alkyls of the type Si_2R_6, Si_3R_8, etc., are generally more difficult to prepare and are much more reactive than simple alkyls. Attempts to prepare alkyl derivatives of Si_2Cl_6 by sodium condensation with organic chlorides results only in fission of the silicon–silicon bond and formation of the corresponding SiR_4 compounds (318), unless the reaction is carried out in two stages according to the plan previously described (320). The regular two-stage Grignard reaction may successfully be employed. The known alkyl and aryl disilanes, together with their physical constants and references to the original papers, are listed in table 2.

B. THE ALKYLSILANES, R_nSiH_{4-n}

The replacement of hydrogen in a silane by alkyl or aryl groups has not been accomplished except by indirect means. Such hydrogen may easily be replaced with halogen, as in the chlorination of monosilane with hydrogen chloride in the presence of aluminum chloride as a catalyst. The halogen may then in turn be replaced by an organic group by the use of the Grignard reaction or by the reaction of other metal alkyls. In this way Stock (347) prepared methylsilane and dimethylsilane, which are listed with the other alkylsilanes in table 3.

The ready availability of trichlorosilane ($SiHCl_3$) has led to the preparation of alkyl derivatives through the application of Grignard reagents. Triethylsilane has also been obtained as a reduction product in the reaction of ethyl silicate with sodium and ethylzinc (203).

Cyanosilane, SiH_3CN, has been obtained by a related synthesis in which iodosilane is first obtained by the action of hydrogen iodide and aluminum iodide on monosilane, and then is treated with silver cyanide to replace the iodine with the cyanide group (290a, p. 33).

C. ORGANOSILANES WITH SUBSTITUTED ALKYL AND ARYL GROUPS

The organic radical of organosilicon compounds is capable of undergoing many of the reactions that are common to hydrocarbons. In general, the organic group may be halogenated, sulfonated, and nitrated under suitably special conditions. The alkylsilanes and alkylhalogenosilanes may be chlorinated by the reaction of sulfuryl chloride in the presence of benzoyl peroxide (330, 332) or by direct chlorination in the presence of phosphorus pentachloride and ultraviolet radiation (361), or with ultraviolet light alone (198). Chlorine so sub-

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[4] The compounds listed in the tables have been arranged in order of increasing complexity of the organic groups. Where two or more dissimilar organic groups appear in the compound, the groups are written in order of increasing complexity and are listed according to the first group. All fluorosilanes are listed in such order of their organic groups, then all chlorosilanes, etc.

TABLE 1

Tetraalkyl- and tetraaryl-silanes, R_4Si

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$(CH_3)_4Si$		26.5	0.646^a		(11, 12, 24, 31, 37, 41, 84, 112, 142, 279, 326, 358, 359, 362)
$(CH_3)_3SiC_2H_5$		62	0.6849^a	1.3820^b	(37, 41, 362)
$(CH_3)_3Si(n\text{-}C_3H_7)$		90	0.7020^a	1.3929^b	(37, 41, 362)
$(CH_3)_3Si(n\text{-}C_4H_9)$		115	0.7181^a	1.4030^b	(37, 362)
$(CH_3)_3Si(i\text{-}C_4H_9)$		108	0.7322^c		(37, 41)
$(CH_3)_3Si(n\text{-}C_5H_{11})$		139	0.7313^a	1.4096^b	(362)
$(CH_3)_3Si(i\text{-}C_5H_{11})$		131.5	0.7322^c		(37, 41)
$(CH_3)_3Si(n\text{-}C_6H_{13})$		163	0.7422^a	1.4154^b	(362)
$(CH_3)_3Si(n\text{-}C_7H_{15})$		184	0.7506^a	1.4201^b	(362)
$(CH_3)_3Si(n\text{-}C_8H_{17})$		202	0.7581^a	1.4242^b	(362)
$(CH_3)_3Si(n\text{-}C_{10}H_{21})$		240	0.7705^a	1.4310^b	(362)
$(CH_3)_3Si(n\text{-}C_{12}H_{25})$		273	0.7800^a	1.4358^b	(362)
$(CH_3)_3Si(n\text{-}C_{14}H_{29})$		300	0.7911^a	1.4410^b	(362)
$(CH_3)_3SiC_6H_5$		171.6	0.873^c		(38, 41, 66)
$(CH_3)_3SiCH_2C_6H_5$		191	0.872^c		(38, 41)
$(CH_3)_2Si(C_2H_5)_2$		95.8	0.7214^c		(37, 41)
$(CH_3)_2Si(C_2H_5)(n\text{-}C_3H_7)$		121	0.7347^c		(37, 41)
$(CH_3)_2Si(C_2H_5)(i\text{-}C_4H_9)$		138	0.7463^c		(37, 41)
$(CH_3)_2Si(n\text{-}C_3H_7)_2$		141.5	0.7414^d		(41)
$(CH_3)_2Si(CH_2)_5$		133.5	0.8039^a	1.4394^e	(39 ,41)
$(CH_3)_2Si(C_6H_5)_2$		177 (45 mm.)			(165)
$(CH_3)_2Si(C_2H_5)(C_6H_5)$		198	0.881^c		(38, 41)
$CH_3Si(C_2H_5)_3$		127	0.7437^a	1.4160^b	(87, 362)
$(CH_3)(C_2H_5)(n\text{-}C_3H_7)\text{-}(C_6H_5)Si$		229			(147, 150)
$(CH_3)(C_2H_5)(n\text{-}C_3H_7)\text{-}(C_6H_5CH_2)Si$		250			(147, 149, 151)
$CH_3Si(C_6H_5)$	67				(192, 222, 223)
$(C_2H_5)_4Si$		153	0.7662^a	1.4268^b	(4, 21, 24, 37, 41, 43, 44, 67, 81, 82, 83, 86, 87, 89, 94, 100, 129, 133, 134, 135, 178, 203, 318, 348, 352, 359, 362)
$(C_2H_5)_3SiCH{=}CH_2$		146			(354)
$(C_2H_5)_3Si(n\text{-}C_3H_7)$		173	0.7724^a	1.4308^b	(38, 41, 43, 44, 66, 362)

TABLE 1—*Continued*

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$(C_2H_5)_3Si(n\text{-}C_4H_9)$		192	0.7786^{a}	1.4348^{b}	(38, 41, 362)
$(C_2H_5)_3Si(i\text{-}C_4H_9)$		187	0.784^{c}		(38, 41, 66)
$(C_2H_5)_3Si(n\text{-}C_5H_{11})$		211	0.7835^{a}	1.4377^{b}	(362)
$(C_2H_5)_3Si(i\text{-}C_5H_{11})$		205	0.785^{c}		(38, 41, 66)
$(C_2H_5)_3Si(n\text{-}C_6H_{13})$		230	0.7880^{a}	1.4400^{b}	(362)
$(C_2H_5)_3Si(n\text{-}C_7H_{15})$		247	0.7907^{a}	1.4422^{b}	(362)
$(C_2H_5)_3Si(n\text{-}C_8H_{17})$		262	0.7971^{a}	1.4438^{b}	(362)
$(C_2H_5)_3Si(n\text{-}C_{10}H_{21})$		293	0.8036^{a}	1.4472^{b}	(362)
$(C_2H_5)_3SiC_6H_5$		239	0.906^{f}		(38, 41, 107, 129, 193, 206, 207)
$(C_2H_5)_3SiCH_2C_6H_5$		268			(193)
$p\text{-}(C_2H_5)_3SiC_6H_4C_2H_5$		118 (18 mm.)	0.8950^{a}		(106)
$p\text{-}(C_2H_5)_3SiC_6H_4Si(C_2H_5)_3$		196 (16.5 mm.)	0.8967^{a}		(106)
$(C_2H_5)_3SiGe(C_6H_5)_3$	93.5				(193)
$(C_2H_5)_2Si(n\text{-}C_3H_7)_2$					(43, 44)
$(C_2H_5)_2Si(CH_2)_5$		184–194			(39, 41)
$(C_2H_5)_2Si(C_6H_5)_2$		297			(129, 173, 206, 207, 208)
$(C_2H_5)_2Si(C_6H_5)(p\text{-}C_6H_4C_2H_5)$		170 (14 mm.)	0.9831^{a}		(106)
$C_2H_5Si(n\text{-}C_3H_7)_3$					(43, 44)
$C_2H_5Si(C_6H_5)_3$	76				(222, 223, 333)
$(C_2H_5)(n\text{-}C_3H_7)(i\text{-}C_4H_9)(C_6H_5CH_2)Si$		283			(174)
$(C_2H_5)(n\text{-}C_3H_7)_2(C_6H_5CH_2)Si$		280			(223)
$(C_2H_5)(n\text{-}C_3H_7)(C_6H_5CH_2)_2Si$		264 (90 mm.)			(46)
$(C_2H_5)(C_6H_{11})_2(C_6H_5)Si$	52–3	*ca.* 370			(52, 173)
$(C_2H_5)(n\text{-}C_3H_7)(C_6H_5)(C_6H_5CH_2)Si$		250			(150)
$(n\text{-}C_3H_7)_4Si$		212	0.7883^{c}		(43, 44, 257, 258, 319, 348, 359)
$(n\text{-}C_4H_9)_4Si$		157 (22 mm.)	0.8008^{a}	1.4465^{b}	(104b, 278, 352)
$(n\text{-}C_5H_{11})_4Si$		318	0.8252^{j}	1.4510^{j}	(318)
$(i\text{-}C_5H_{11})_4Si$		275			(351)
$C_{12}H_{28}Si$		208			(258)
$(C_6H_5)_4Si$	233	428 (*cf.* reference 212b)			(19, 48, 69, 98, 99, 129, 192, 217, 218, 220, 272, 273, 318, 319, 320, 321, 327, 348)

TABLE 1—*Concluded*

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$(C_6H_5CH_2)_4Si$	127.5		1.0776^k		(218, 247, 272, 333, 334)
$(m\text{-}CH_3C_6H_4)_4Si$	150.8		1.1188^k		(273, 319)
$(p\text{-}CH_3C_6H_4)_4Si$	228		1.0793		(48, 272, 273, 319)
$(p\text{-}C_6H_5C_6H_4)_4Si$	274				(48, 318)
$(C_4H_3S)_4Si$	135.5				(195)

a, d_4^{20}; b, n_D^{20}; c, d_4^{15}; d, $d_4^{17.6}$; e, $n_D^{20.1}$; f, d_{15}^{15}; g, d_4^{22}; h, n_D^{22}; i, d_4^{32}; j, n_D^{25}; k, d^{20}.

TABLE 2

Organopolysilanes

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$[(CH_3)_3Si]_2$	14.0–14.4	113	0.7230^d	1.4207^e	(24, 30, 38, 41)
$[(C_2H_5)_3Si]_2$		252	0.8403^a		(67, 90, 93, 94, 95, 193)
$[(C_2H_5)(n\text{-}C_3H_7)(C_6H_5)Si]_2$		268 (100 mm.)			(161)
$(C_2H_5)_2(C_6H_5)_8Si_4$	253–4				(162)
$[(n\text{-}C_3H_7)_3Si]_2$		114 (3 mm.)	0.8693^b	1.4740^c	(319)
$[(C_6H_5)_3Si]_2$	352				(154, 192, 316, 319, 320)
$(C_6H_5)_8Si_4$	>300				(186)
$(C_6H_5)_8Si_4I_2$	>250				(186)
$(C_6H_5)_8Si_4Cl_2$	180				(186)
$(C_6H_5)_8Si_4O$	*ca.* 225				(186)
$(C_6H_5)_8Si_4O_2$	*ca.* 245				(186)
	ca. 222				(186)
$[(C_6H_5CH_2)_3Si]_2$	194				(320)
$[(p\text{-}CH_3C_6H_4)_3Si]_2$	345				(319)
$[(p\text{-}CH_3C_6H_4)_2Si]_4$	310				(341)
	292				(341)
$[(p\text{-}CH_3C_6H_4)_2Si]_4O$	228–9				(341)
$[(p\text{-}CH_3C_6H_4)_2Si]_4I_2$	300 dec.				(341)

a, d_{20}^{20}; b, d_4^{20}; c, n_D^{20}; d, $d_4^{24.4}$; e, $n_D^{24.4}$.

stituted may be replaced by iodine by means of the sodium iodide reagent (361). The (chloromethyl)silanes and siloxanes undergo hydrolytic cleavage in the presence of alkaline catalysts to give halogenomethanes and siloxanes (198, 198a). In contrast to this reaction the carbon-chlorine bond of β-chloroethyltrichlorosilane reacts quantitatively with dilute alkali (332):

$$ClCH_2CH_2SiCl_3 \xrightarrow[H_2O]{OH^-} CH_2{=}CH_2 + Si(OH)_4 + 4Cl^-$$

The beta chlorine can be removed by dehydrohalogenation using dry quinoline without cleavage of the carbon-silicon bond, in this way forming vinyl derivatives (117). A chlorine in the gamma position, while it can not be titrated, undergoes reaction with alcoholic caustic at room temperature, yielding cyclopropane in the case of γ-chloropropyltrichlorosilane (330).

Organosilanes containing halogenated aryl groups may be prepared by direct halogenation (292) or by an indirect synthesis in which a bromohalogenobenzene is allowed to react with magnesium to form the halogenophenylmagnesium bromide, which, in turn, reacts with silicon tetrachloride to form a halogenochlorophenylsilane (35a, 106, 107). The chlorine attached to silicon in these compounds may be replaced by other organic groups by further Grignard synthesis (106, 107). When the halogen that occurs in a halogenophenyltrialkylsilane is bromine it may react with magnesium to give the corresponding Grignard reagent (106, 107). This Grignard reagent is then capable of reaction with aldehydes to give the corresponding alcohols, or with other organometallic compounds to give condensation products.

TABLE 3

Organomonosilanes, R_nSiH_{4-n}

COMPOUND	MELTING POINT	BOILING POINT	d	REFERENCES
	°C.	°C.		
CH_3SiH_3	−157	−57	0.62[a]	(347, 366)
$(CH_3)_2SiH_2$	−150	−20	0.68[b]	(347, 366)
$(CH_3)_3SiH$		9		(349)
$(C_2H_5)_3SiH$		107		(203)
$(n\text{-}C_3H_7)_3SiH$		107-1	0.7621[c]	(257, 258)
$(i\text{-}C_4H_9)_3SiH$		205		(351)
$(i\text{-}C_5H_{11})_3SiH$		245		(351)
$(C_6H_5)_3SiH$	202			(192, 208, 281)
$(C_6H_5CH_2)_3SiH$	91			(75, 272)
$(C_6H_{11})_2(C_6H_5)SiH$		182 (4 mm.)		(52)

a, d^{-57}; b, d^{-80}; c, d^{15}_{4}.

Kipping succeeded in nitrating the phenyl group of a number of organosilicon compounds (170, 173, 178, 356), and found that in general most of the nitration occurred in the meta position. He reduced these nitro compounds to the corresponding amines and formed derivatives of these (171, 173) with acetic acid and acetone. The phenyl and benzyl groups attached to silicon have both been sulfonated with sulfuric acid (41, 42, 46, 47, 148, 149, 150, 151, 152, 153, 154, 161, 174, 179, 215, 216, 222, 223). A list of these compounds, with the references to the original papers, is given in table 4.

D. ALKYL- AND ARYL-HALOGENOSILANES, R_nSiX_{4-n}

The organosilicon halides or alkylhalogenosilanes have been popular as intermediates for the preparation of a great many of the organosilicon compounds,

TABLE 4

Organosilanes with substituted alkyl and aryl groups

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$(CH_3)_3SiCH_2Cl$		97.1	0.8791^a	1.4180^b	(361)
$(CH_3)_3SiCH_2I$		139.5	1.4431^a	1.4917^b	(361)
$(CH_3)_3SiCH_2HgCl$	75				(361)
$(CH_3)_3SiCHClCH_3$		117.8		1.4242^b	(332)
$(CH_3)_3SiCH(HgCl)CH_3$	97				(332)
p-$(CH_3)_3SiCH_2C_6H_4$-SO_3H	116				(41, 42)
p-$(CH_3)_3SiCH_2C_6H_4$-SO_2Cl	46				(41, 42)
p-$(CH_3)_3SiCH_2C_6H_4$-SO_2Br	60.5				(41, 42)
p-$(CH_3)_3SiCH_2C_6H_4$-SO_2NH_2	81.5				(41, 42)
p-$(CH_3)_3SiCH_2C_6H_4$-SO_2NHCH_3	77				(41, 42)
p-$(CH_3)_3SiCH_2C_6H_4$-$SO_2NHC_6H_5$	125				(41, 42, 371)
p-$(CH_3)_3SiCH_2C_6H_4SO_2$-$N(CH_3)(C_6H_5)$	72				(41, 42)
p-$(CH_3)_3SiCH_2C_6H_4SO_2$-$NHCH_2C_6H_5$	131				(41, 42)
p-$(CH_3)_3SiCH_2C_6H_4SO_2$-$NH($o-$C_6H_4CH_3)$	153				(41, 42)
p-$(CH_3)_3SiCH_2C_6H_4SO_2$-$NH($p-$C_6H_4CH_3)$	98				(41, 42)
$(C_2H_5)_3SiCH_2CH_2Cl$		80 (9 mm.)	0.9158	1.4562	(83, 86, 87, 253, 354)
$(C_2H_5)_3SiCHClCH_3$		72 (9 mm.)	0.9147	1.4538	(354)
$(C_2H_5)_3SiCH_2CHCl_2$		208			(87)
$(C_2H_5)_3SiCH_2CH_2OH$		190			(87, 253)
$(C_2H_5)_3SiCH_2CH_2OC$-OCH_3		211			(87, 253)
p-$(C_2H_5)_3SiC_6H_4Cl$		137 (14.5 mm.)	1.0056^c	1.5219^d	(107)
p-$(C_2H_5)_3SiC_6H_4Br$		149 (14 mm.)	1.1652^a	1.5332^b	(107)
p-$(C_2H_5)_3SiC_6H_4I$		165 (13 mm.)	1.3304^a	1.5623^b	(107)
$(C_2H_5)_3SiC_6H_4NO_2$		307			(173)
p-$(C_2H_5)_3SiC_6H_4Pb(CH_3)$		191 (17 mm.)	1.3997^e	1.5494^f	(107)
p-$(C_2H_5)_3SiC_6H_4Sn$-$(C_2H_5)_3$		214 (18 mm.)	1.1216^g	1.5276^h	(107)
p-$(C_2H_5)_3SiC_6H_4As$-$(C_6H_5)_2$		280 (17 mm.)	1.1661^i	1.6146^j	(107)
[p-$(C_2H_5)_3SiC_6H_4As$-$(C_6H_5)_2]\cdot HgCl_2$	188				(107)
[p-$(C_2H_5)_3SiC_6H_4As$-$(C_6H_5)_2]\cdot HgBr_2$	181				(107)
[p-$(C_2H_5)_3SiC_6H_4As$-$(C_6H_5)_2]\cdot HgI_2$	139.5				(107)

TABLE 4—*Concluded*

COMPOUND	FREEZING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
p-$(C_2H_5)_3SiC_6H_4CHOH$-CH_3		174 (14.5 mm.)	0.9596^a		(106)
p-$(C_2H_5)_3SiC_6H_4CHOH$-CH_2CH_3		185 (16.5 mm.)	0.9575^a		(106)
p-$(C_2H_5)_3SiC_6H_4CHOH$-$(CH_2)_2CH_3$		200 (21 mm.)	0.9491^a		(106)
p-$(C_2H_5)_3SiC_6H_4CHOH$-$CH(CH_3)_2$		191 (18 mm.)	0.9512^a		(106)
$(C_2H_5)_2(C_6H_5)(p$-$BrC_6H_4)Si$		203 (13.7 mm.)	1.2153^a		(106)
$(C_2H_5)_2Si(m$-$C_6H_4NO_2)_2$	103				(173)
$(C_2H_5)_2Si(m$-$C_6H_4NH_2)_2$	90				(173)
$(C_2H_5)_2Si(m$-C_6H_4NH-$COCH_3)_2$	164				(173)
p-$(n$-$C_3H_7)_3SiC_6H_4Cl$		160 (14 mm.)	0.9708^k	1.5123^l	(107)
$(m$-$C_6H_4NO_2)_4Si$	256				(170, 178, 356)
$(m$-$C_6H_4NH_2)_4Si$	380 dec.				(171)
$(m$-$C_6H_4NHCOCH_3)_4Si$	301				(171)
$[m$-$C_6H_4NHCH(CH_3)_2]_4Si$	135				(171)
$C_{12}H_{27}BrSi$		138 (60 mm.)			(258)

a, d_4^{20}; b, n_D^{20}; c, $d_4^{9.6}$; d, $n_2^{9.6}$; e, $d_4^{23.4}$; f, $n_D^{23.4}$; g, $d^{21.2}$; h, $n_D^{21.2}$; i, $d_4^{21.3}$; j, $n_D^{21.3}$; k, d_4^9; l, n_D^9

See also chlorine-substituted organosiloxanes and halogenosilanes in their respective tables

because the halogen atoms easily undergo replacement reactions as well as hydrolysis and ammonolysis. Synthesis by the stepwise replacement of the halogen atoms in a silicon halide has already been discussed, and also the preparation by the direct reaction of hydrocarbon halides with elementary silicon. The properties of the known compounds and the references to the original papers are listed in table 5. The change of boiling point with consecutive replacement of chlorine atoms in silicon tetrachloride by methyl, ethyl, and propyl groups is shown in figure 1.

1. *Properties of the organochlorosilanes*

The trialkylchlorosilanes, R_3SiCl, are sources of the hexaalkyldisiloxanes and disilazanes through reaction of such chlorides with water or ammonia. Under special conditions the hydrolysis to silanols of the type R_3SiOH has been accomplished without the simultaneous condensation of such silanols to the corresponding disiloxanes (307).

The dialkyldihalogenosilanes are the intermediates from which the linear silicon polymers are made, and therefore have been of particular importance (290a). Their preparation by the direct reaction has already been discussed. Most of the other methods of synthesis may also be applied, with yields that are somewhat higher than would be expected from theory (95b); it appears that the

TABLE 5

Organohalogenosilanes

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
Fluorosilanes					
	°C.	°C.			
CH_3SiF_3	−72.8	−30.2			(24d, 268)
$(CH_3)_2SiF_2$	−87.5	2.7			(24g, 268)
$(CH_3)_3SiF$	−74.3	16.4			(24g, 252a)
$C_2H_5SiF_3$	−113.3	−4.2			(24b, 73)
$(C_2H_5)_2SiF_2$	−78.7	60.9			(73)
$(C_2H_5)_3SiF$		109	0.8354^a	1.3900^b	(77, 78, 100)
n-$C_3H_7SiF_3$		24.9			(24c)
$(n$-$C_3H_7)_3SiF$		175	0.8339^a	1.4107^b	(100)
i-$C_3H_7SiF_3$	−127.6	15.7			(24f)
n-$C_4H_9SiF_3$	−96.9	52.4	1.006^c		(24e, 268)
$(n$-$C_4H_9)_2SiF_2$		154	0.9048^c		(268)
$(n$-$C_4H_9)_3SiF$		224	0.8372^a	1.4250^b	(100, 268)
n-$C_5H_{11}SiF_3$		77	0.9923^c		(268)
$(n$-$C_5H_{11})_2SiF_2$		193	0.8972^c		(268)
$(n$-$C_5H_{11})_3SiF$		267	0.8389^a	1.4305^b	(100, 268)
$C_6H_5SiF_3$		102	1.201		(73, 268)
$(C_6H_5)_2SiF_2$		247	1.155		(73, 268)
$(C_6H_5)_3SiF$	64	205 (10 mm.)			(218)
$(C_6H_5CH_2)_3SiF$	79	235.5			(247)
CH_3SiF_2Cl	*ca.* −110	*ca.* −0.5			(24d)
CH_3SiFCl_2	−98.7	29.5			(24d)
$(CH_3)_2SiFCl$	−85.1	36.4			(24g)
$C_2H_5SiF_2Cl$	s	27.2			(24b)
$C_2H_5SiFCl_2$	s	62.2			(24b)
n-$C_3H_7SiF_2Cl$	s	55–57 (745 mm.)			(24c)
n-$C_3H_7SiFCl_2$	s	88–89 (745 mm.)			(24c)
i-$C_3H_7SiF_2Cl$	s	48.8			(24f)
i-$C_3H_7SiFCl_2$	s	84.0			(24f)
n-$C_4H_9SiF_2Cl$	s	84.0			(24e)
n-$C_4H_9SiFCl_2$	s	116.1			(24e)
Chlorosilanes					
CH_3SiHCl_2	−93	41	1.105^e		(313a, 347)
CH_3SiH_2Cl	−134	8			(347, 366)
CH_3SiCl_3	−77.8	65.7			(24d, 32, 101, 293)
$(CH_3)_2SiCl_2$	−76.1	70.0	1.06^d		(24g, 32, 101, 128, 293)
$(CH_3)_3SiCl$	−57.7	57.3	0.8536^e		(24g, 102, 214, 237, 293, 349)

TABLE 5—*Continued*

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
Chlorosilanes—*Continued*					
	°C.	°C			
$(CH_3)_2(CH_2Cl)SiCl$		115			(198)
$(CH_3)(CH_2Cl)_2SiCl$		172			(198)
$(CH_3)_2(CHCl_2)SiCl$		149.5			(198)
$(CH_3)_2SiCl(OC_4H_9(n))$		142			(308)
$(CH_3)(CH_2Cl)SiCl_2$		121.3			(198)
$(CH_3)(CHCl_2)SiCl_2$		107.5 (225 mm.)			(198)
$(CH_3)(CCl_3)SiCl_2$	99	109 (150 mm.)			(198)
$(CH_3)(CH_3CHCl)SiCl_2$		136			(117)
$(CH_3)(CH_2ClCH_2)SiCl_2$		157			(117)
$(CH_3)(CH_2{=}CH)SiCl_2$		93	1.085^f		(117)
$(CH_3)_2(CH_2{=}CHCH_2)SiCl$		113	0.922^g		(117)
$(CH_3)(CH_2{=}CHCH_2)SiCl_2$		120	1.057^g		(117)
$Cl[(CH_3)_2SiO]Si(CH_3)_2Cl$	−37	138	1.038^h		(266)
$Cl[(CH_3)_2SiO]_2Si(CH_3)_2Cl$	−53	184	1.018^h		(266)
$Cl[(CH_3)_2SiO]_3Si(CH_3)_2Cl$	−62	222	1.011^h		(266)
$Cl[(CH_3)_2SiO]_4Si(CH_3)_2Cl$	*ca.* −80	138 (20 mm.)	1.005^h		(266)
$Cl[(CH_3)_2SiO]_5Si(CH_3)_2Cl$	*ca.* −80	161 (20 mm.)	1.003^h		(266)
$(CH_3)(C_6H_5)SiCl_2$		82.5 (13 mm.)	1.1876^d		(128)
$C_2H_5SiCl_3$	−105.6	97.9	1.2388^i		24b, 41, 91, 149, 203)
$C_2H_5SiCl(OC_2H_5)_2$		151			(203)
$(C_2H_5)_2SiCl_2$	−96.5	129	1.106^j		(2, 41, 128, 203, 231)
$(C_2H_5)_2SiCl(OC_2H_5)$		147			(199, 203)
$(C_2H_5)_3SiCl$		143.5	0.9249		(78, 200, 203, 231)
$(C_2H_5)(n\text{-}C_3H_7)SiCl_2$		153	1.0420^k		(37, 41)
$(C_2H_5)(i\text{-}C_4H_9)SiCl_2$		169	1.0235^h		(37, 41)
$CH_2ClCH_2SiCl_3$		152			(117, 332)
$CH_3CHClSiCl_3$		138			(117, 332)
$(C_2H_5)(n\text{-}C_3H_7)(C_6H_5)SiCl$		178 (100 mm.)			(147, 150, 161)
$(C_2H_5)(n\text{-}C_3H_7)(C_6H_5CH_2)\text{-}SiCl$		195 (100 mm.)			(146, 147, 151, 161)
$(C_2H_5)(i\text{-}C_4H_9)(C_6H_5CH_2)\text{-}SiCl$		200 (100 mm.)			(215)

TABLE 5—*Continued*

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
Chlorosilanes—*Continued*					
	°C.	°C.			
$(C_2H_5)(C_6H_5)SiCl_2$		230	1.159^l		(38, 41, 128, 146, 150)
$(C_2H_5)(C_6H_5)_2SiCl$		207 50 mm.			(147, 222, 223)
$(C_2H_5)(C_6H_5CH_2)SiCl_2$		169 (100 mm.)			(147, 151, 215, 282, 368)
$(C_2H_5)(C_6H_5CH_2)_2SiCl$		246 (100 mm.)			(46, 282)
p-$(C_2H_5)_3SiC_6H_4SiCl_3$		175 (13.5 mm.)			(106)
$CH_2{=}CHSiCl_3$		92	1.264^e		(117)
$(CH_2{=}CH)_2SiCl_2$		119	1.088^e		(117)
n-$C_3H_7SiCl_3$		122.7	1.1967^h		(24c, 41, 246, 249, 330)
$(n$-$C_3H_7)_2SiCl_2$		175	1.035^l		(41)
i-$C_3H_7SiCl_3$	−87.7	119.4			(24f)
$C_2H_5CHClSiCl_3$		157			(330)
$CH_3CHClCH_2SiCl_3$		162			(330)
$CH_2ClC_2H_4SiCl_3$		178.5			(330)
$CH_2{=}CHCH_2SiCl_3$		117.5	1.211^e		(117)
$(CH_2{=}CHCH_2)HSiCl_2$		97	1.086^e		(117)
$(CH_2{=}CHCH_2)_2SiCl_2$		166 (83 mm.)			(117)
n-$C_4H_9SiCl_3$		148.9	1.1623^m		(24e, 37, 41)
i-$C_4H_9SiCl_3$		141	1.154^h		(37, 41)
i-$C_4H_9SiCl(OCH_3)(OC_2H_5)$		155			(178)
n-$C_5H_{11}SiCl_3$		107 (120 mm.)			(362)
i-$C_5H_{11}SiCl_3$		46 (9 mm.)			(41, 249)
$(CH_2)_5SiCl_2$		170	1.1560^h	1.4697^o	(39, 41)
n-$C_6H_{13}SiCl_3$		127 (98 mm.)			(362)
$C_6H_{11}SiCl_3$		210			(256)
$(C_6H_{11})_2SiCl_2$		150 (4 mm.)			(256)
$(C_6H_{11})(C_6H_5)SiCl_2$		124 (0.5 mm.)			(51)
$(C_6H_{11})_2(C_6H_5)SiCl$	47	190 (2 mm.)			(51)
n-$C_8H_{17}SiCl_3$		119 (28 mm.)			(362)

TABLE 5—*Continued*

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
		Chlorosilanes—*Continued*			
	°C.	°C.			
$n\text{-}C_{10}H_{21}SiCl_3$		183 (84 mm.)			(362)
$n\text{-}C_{12}H_{25}SiCl_3$		120 (3 mm.)			(362)
$n\text{-}C_{14}H_{29}SiCl_3$		156 (3 mm.)			(362)
$Cl_3SiCH_2SiHCl_2$		52 (10 mm.)			(263)
$(Cl_3Si)_2CH_2$		64 (10 mm.)			(263)
$[Cl_2SiCH_2]_3$	81-82.5	130 (10 mm.)			(263, 264)
$[Cl_2SiCH_2]_n$, $(n>3)$		200 (10 mm.)			(263)
$(Cl_3SiCH_2)_2$	27-9	93 (25 mm.)			(263)
$[(CH_3CO)_2CH]_3SiCl$	96-8 dec.				(305)
$C_6H_5SiCl_3$		201.5	1.3256^m		(41, 204, 207, 245, 250, 289, 302, 320)
$(C_6H_5)_2SiCl_2$		305.2			(128, 159, 180, 289, 302, 321)
$(C_6H_5)_2SiCl(OC_6H_5)$		253 (40 mm.)			(167)
$(C_6H_5)_3SiCl$	88-9	378			(178, 194, 223, 273, 302)
$p\text{-}ClC_6H_4SiCl_3$		105 (15 mm.)			(107)
$p\text{-}BrC_6H_4SiCl_3$		123 (15 mm.)			(107)
$(p\text{-}BrC_6H_4)_2SiCl_2$		239 (21 mm.)			(107)
$(C_6H_5)(C_6H_5CH_2)SiCl_2$		318			(224, 286)
$(C_6H_5)(p\text{-}BrC_6H_4)SiCl_2$		200 (4 mm.)	1.5005^h		(106)
$[Cl(C_6H_5)_2Si]_2O$	38	240 (1 mm.)			(35)
$Cl[(C_6H_5)_2SiO]_2Si(C_6H_5)_2Cl$		300 (1 mm.)			(35)
$C_6H_5CH_2SiCl_3$		216	1.2889^p		(38, 41, 231, 246, 249)
$(C_6H_5CH_2)_2SiCl_2$	50-2	243 (100 mm.)			(231)

TABLE 5—*Concluded*

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
		Chlorosilanes—*Concluded*			
	°C.	°C.			
$(C_6H_5CH_2)_3SiCl$	14				(231, 282)
$C_6H_4CHClSiCl_3$		162 (75 mm.)			(332)
p-$CH_3C_6H_4SiCl_3$		219			(206, 207, 271)
$(p$-$CH_3C_6H_4)_2SiCl_2$		238 (50 mm.)			(271, 341)
$(p$-$CH_3C_6H_4)_3SiCl$	116				(340)
α-$C_{10}H_7SiCl_3$		168 (22 mm.)	1.3760		(249)
$(C_6H_5)_8Si_4Cl_2$	180				(186)
		Bromosilanes			
CH_3SiBr_3		133.5			(289)
$(CH_3)_2SiBr_2$		112.3			(289)
$(CH_3)_3SiBr$		80	1.189^h		(101a)
$(C_2H_5)_3SiBr$		66.5 (24 mm.)	1.1766^h		(78, 87, 106 193)
$(n$-$C_3H_7)_3SiBr$		213			(257, 258)
$(i$-$C_4H_9)_3SiBr$		245			(351)
$(i$-$C_5H_{11})_3SiBr$		279			(351)
$(C_6H_5)_2SiBr_2$		180 (12 mm.)			(208, 289)
$(C_6H_5)_3SiBr$	119				(192, 208)
		Iodosilanes			
$(C_6H_5)_8Si_4I_2$	>250				(186)
$[(p$-$CH_3C_6H_4)_2Si]_4I_2$	300 dec.				(341)

a, d_4^{25}; b, n_D^{25}; c, $d_4^{26.5}$; d, d_{25}^{25}; e, d_{27}^{27}; f, d_{27}^{25}; g, d_{27}^{27}; h, d_4^{20}; i, $d_4^{19.4}$; j, d^{15}; k, $d_4^{20.7}$; l, d_4^{15}; m, $d_4^{18.8}$; n, $n_D^{20.2}$; p, $d_4^{19.3}$; r, d^0; s, forms glass.

symmetry of the actions of the dihalosilanes decreases their reactivity toward alkylating reagents. Hydrolysis of the dialkyldihalosilanes yields corresponding silanediols of the type $R_2Si(OH)_2$, which can be isolated if the condensation to a siloxane does not proceed rapidly at room temperature. In general, the larger the organic group the slower will be that condensation. Strong acids and alkalies are known to have a marked catalytic effect on the condensation (35, 159).

The alkyltrihalogenosilanes, $RSiX_3$, are by-products of the direct reaction and may be obtained by the substitution of a single chlorine atom in silicon tetrachloride. These substances hydrolyze very readily to form the corresponding silanetriols, $RSi(OH)_3$. These silanetriols condense very readily to highly polymeric or cross-linked products rather than to the so-called "siliconic acids" of the type RSiOOH, as was originally supposed (245).

The formation of alkylhalogenosilanes with unsaturated organic groups requires special methods. Trichlorovinylsilane may be made by the direct reaction of vinyl chloride with silicon (117), but the yields are relatively poor because of the pyrolysis of vinyl chloride at the temperature of the reaction. It is more convenient first to prepare trichloroethylsilane, and then to chlorinate this compound to give trichloro(chloroethyl)silane, followed by dehydrohalogenation to leave trichlorovinylsilane (117). Such removal of hydrogen chloride is aided by the action of a tertiary amine such as quinoline. Of course the absorption of unsaturated hydrocarbons by silicon tetrachloride (325) is particularly suited to the preparation of such unsaturated halogenosilanes (see table 5).

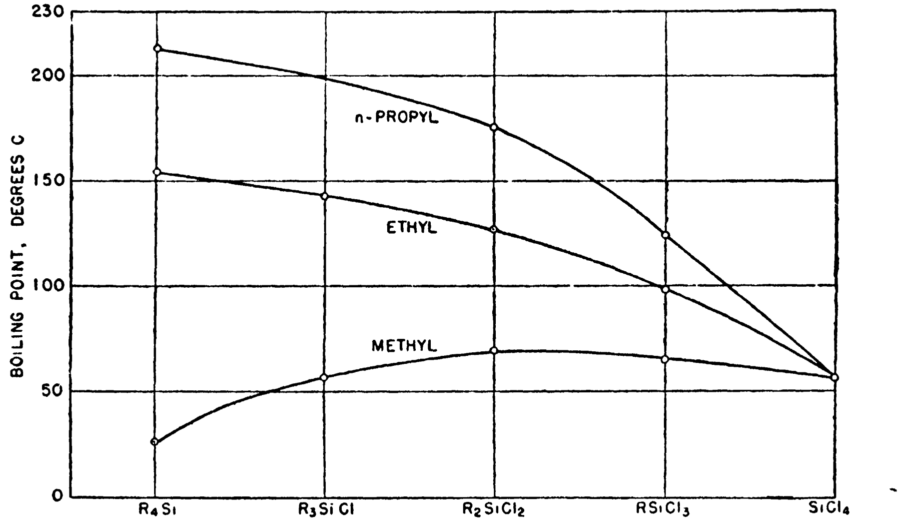


FIG. 1. Change in boiling points with successive replacement of chlorine atoms by alkyl groups.

2. *Properties of the organochlorofluorosilanes*

The physical properties of organochlorofluorosilanes as shown in table 5 are seen to be intermediate between those of the corresponding fluorosilanes and chlorosilanes. Swarts observed that the replacement of chlorine in a polychlorinated organic compound by fluorine gave a regular, almost constant, lowering of the boiling point. From the following table (p. 119), it is clear that the Swarts rule is applicable to the alkyltrichlorosilanes.

The solubilities of the chlorofluorosilanes in organic solvents resemble those of the organofluorosilanes. They all hydrolyze, but more slowly with increasing fluorine content and with increasing size of the organic radical. It is thought probable from the behavior of the *n*-butyl compounds that the silicon–chlorine bond is more susceptible to solvolysis than is the silicon–fluorine bond (24e).

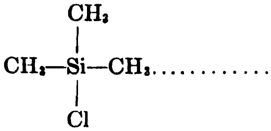
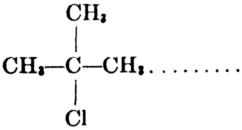
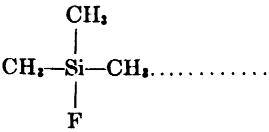
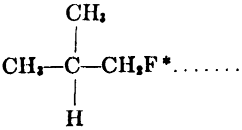
Boiling-point differences of ethyl- and isopropyl-trihalogenosilanes

COMPOUND	BOILING POINT	DIFFERENCE	AVERAGE
	°C.	°C.	
$C_2H_5SiCl_3$	97.9		34.1
		35.7	
$C_2H_5SiCl_2F$	62.2		
		35.0	
$C_2H_5SiClF_2$	27.2		
		31.0	
$C_2H_5SiF_3$	−4.2		
i-$C_3H_7SiCl_3$	119.4		34.5
		35.4	
i-$C_3H_7SiCl_2F$	84.0		
		35.2	
i-$C_3H_7SiClF_2$	48.8		
		33.1	
i-$C_3H_7SiF_3$	15.7		

This suggests that it might be possible to achieve only partial alcoholysis of the n-butylchlorofluorosilanes with the production of mixed alkoxyfluorosilanes.

In the absence of moisture, alkylchlorofluorosilanes seem to be inert to iron, steel, copper, platinum, mercury, and nichrome (24e).

If one considers the alkylhalogenosilanes as carbon compounds in which an atom of silicon has replaced an atom of carbon, it is surprising to note the slight effect on the boiling point which this replacement has, as shown in the following table.

FORMULA	BOILING POINT	FORMULA	BOILING POINT
	°C.		°C.
$CH_3SiCl_2CH_3$	70.0	$CH_3CCl_2CH_3$	69.7
$CH_3SiClFCH_3$	36.4	$CH_3CClFCH_3$	35.0
$CH_3SiF_2CH_3$	2.7	$CH_3CF_2CH_3$	−0.6 to −0.2
 $CH_3\text{—}\underset{\underset{Cl}{\vert}}{\overset{\overset{CH_3}{\vert}}{Si}}\text{—}CH_3$	57.3	 $CH_3\text{—}\underset{\underset{Cl}{\vert}}{\overset{\overset{CH_3}{\vert}}{C}}\text{—}CH_3$	51-52
 $CH_3\text{—}\underset{\underset{F}{\vert}}{\overset{\overset{CH_3}{\vert}}{Si}}\text{—}CH_3$	16.4	 $CH_3\text{—}\underset{\underset{H}{\vert}}{\overset{\overset{CH_3}{\vert}}{C}}\text{—}CH_2F$ *	16

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* The corresponding carbon analog could not be found. This compound is nearly analogous.

3. *Properties of the organofluorosilanes*

The physical properties of organofluorosilanes are shown in table 5. The change in boiling points with successive replacements of fluorine atoms by alkyl groups is shown in figure 2.

In the liquid state the alkylfluorosilanes are colorless mobile liquids, soluble in petroleum ether (77), benzene, toluene, various chlorinated organic solvents, such as carbon tetrachloride, tetrachloroethylene, chlorobenzene, dichlorobenzene, ether, and ethyl acetate (24c, 24e, 100, 333).

The thermal stability of organofluorosilanes is remarkable. Trifluoromethylsilane is quite stable at 400°C. and decomposes only slowly at 600°C. Even dibutyldifluorosilane can be heated in a glass tube to 300°C. without apparent decomposition (268).

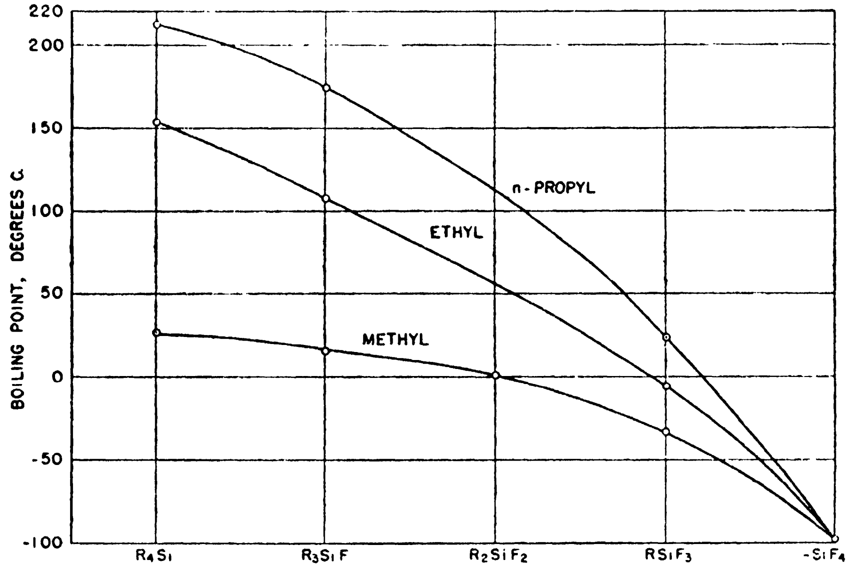

FIG. 2. Change in boiling points with successive replacement of fluorine atoms by alkyl groups.

In general, the organofluorosilanes differ from the other halosilanes in being more difficult to hydrolyze. This resistance to hydrolysis increases with replacement of fluorine by alkyl groups; for example, ethyltrifluorosilane fumes in moist air and hydrolyzes immediately in contact with water (73), while diethyldifluorosilane sinks in water as oily drops and only after 12 hr. standing does a thin film of hydrolysis products appear at the interface. Triethylfluorosilane is even more resistant to hydrolysis. However, all three are quickly hydrolyzed in basic solutions.

Similarly, in an alkyltrifluorosilane, increase in the size of the alkyl group retards hydrolysis. In methyl-, ethyl-, and propyl-trifluorosilanes the odor of the compounds is masked by that of the hydrolytic product, hydrogen fluoride, while in the case of *n*-butyltrifluorosilane, hydrolysis is so slow that the peculiar sharp suffocating odor of the compound itself can be recognized.

When *n*-butyltrichlorosilane is added to acetone, it slowly reacts to give a deep red solution, probably containing mesityl oxide and phorone, a condensation produced by the hydrolytic products of the silane, whereas no reaction takes place with *n*-butyltrifluorosilane (24e).

Similarly, *n*-butyltrichlorosilane readily undergoes alcoholysis but *n*-butyltrifluorosilane merely dissolves in the alcohol (24e).

It is reported that fluorotriphenylsilane is unreactive with water (248), whereas the corresponding chlorotriphenylsilane is hydrolyzed by ice water acidified with sulfuric acid to give triphenylsilanol (191). The corresponding bromo and iodo compounds are rapidly attacked by water (193, 208). Trifluorophenylsilane is quickly hydrolyzed by water, but difluorodiphenylsilane is not hydrolyzed in moist air and even in contact with water only a trace of hydrolytic product appears after a day. Alkalies hydrolyze these two quickly.

In general, the triorganomonofluorosilanes of higher molecular weight are not even readily hydrolyzed by aqueous bases, nor do they react with sodium dissolved in liquid ammonia (100, 268).

Tests so far reveal no tendency of alkyltrifluorosilanes to coördinate with a metal fluoride (24b, 24d), as is the reaction of silicon tetrafluoride.

Halogenation of trialkylfluorosilanes (78) goes in the main as follows:

$$R_3SiF + X'_2 \rightarrow R_2SiFX' + RX'$$

but the reaction is complicated by halogenation of R by hydrogen substitution. The organofluorosilanes give no reaction, at temperatures up to their boiling points, with mercury, nichrome, and iron (24b-24g).

E. THE ALKYLALKOXY- AND AROXY-SILANES, $R_nSi(OR')_{4-n}$

Closely related to the organosilicon halides are the alkyl-and aryl-substituted silicon ethers. While these compounds may be prepared by the reaction of the corresponding chlorosilanes with alcohols or phenols, they may also be prepared by the reaction of the appropriate Grignard reagent with an orthosilicate having the desired R′ groups. The resulting alkylalkoxysilanes are colorless liquids of pleasant odor, capable of many of the reactions of the corresponding halosilanes. The ether groups are readily removed by hydrolysis in the presence of strong mineral acids, and much more slowly in pure water. Hydrolysis yields the same silanols as are obtained by the hydrolysis of the corresponding halosilanes; hence the organic-substituted silicon ethers also are satisfactory intermediates for the preparation of silicon polymers through condensation of silanols (8, 10, 234).

A list of the known alkoxy- and aroxy-organosilanes, together with their properties and the references to the original preparations, is given in table 6.

F. ORGANOSILANOLS, $R_nSi(OH)_{4-n}$, ETC.

The formation of silanols by the hydrolysis of halogenosilanes and alkoxy-

TABLE 6

Alkoxy- and aroxy-organosilanes

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$(CH_3)_3SiOCH_3$		57.2		1.3679^a	(307)
$(CH_3)_3SiOC_2H_5$		75.0	0.7573^b	1.3741^a	(54, 307)
$(CH_3)_3SiOC_2H_4Cl$		134.3	0.9443^b	1.4140^a	(262, 312)
$(CH_3)_3SiOC_4H_9(n)$		124.6	0.7774^b	1.3925^a	(307)
$(CH_3)_2Si(OC_2H_5)_2$		111	0.890^b	1.3839^a	(234, 278)
$(CH_3)_2Si(OC_2H_4Cl)_2$		213	1.135^b	1.4420^a	(262, 312)
$(CH_3)_2Si(OC_2H_4Br)_2$		92 (2.5 mm.)			(262)
$(CH_3)_2Si(OC_4H_9(n))_2$		187	0.8434^b	1.4058^a	(308)
$(CH_3)_2Si(OC_4H_9(n))Cl$		142			(308)
$CH_3Si(OC_2H_5)_3$		151	0.938^b	1.3869^a	(205, 207, 278)
$CH_3Si(OC_2H_4Cl)_3$		137 (6 mm.)	1.257^b	1.4562^a	(262, 312)
$CH_3Si(OC_2H_4Br)_3$		131 (1 mm.)			(262)
$CH_3SiH(OC_2H_4Cl)_2$		96 (18 mm.)	1.1643^b	1.4431^a	(262, 312)
$CH_3Si(OC_4H_9(n))_3$		115 (10 mm.)	0.8775^b	1.4106^a	(308)
$[n\text{-}C_4H_9OSi(CH_3)_2]_2O$		225	0.8733^b	1.4051^a	(308)
$[n\text{-}C_4H_9O][(CH_3)_2SiO]_3C_4H_9(n)$.		125 (10 mm.)	0.8932^b	1.4053^a	(308)
$(C_2H_5)_3SiOC_2H_5$		153	0.8414		(199, 203)
$(C_2H_5)_2Si(OC_2H_5)_2$		155	0.8752^c		(199, 203)
$(C_2H_5)_2SiCl(OC_2H_5)$		147			(199, 203)
$C_2H_5Si(OCH_3)_3$		126	0.9747^c		(202, 207)
$C_2H_5Si(OC_2H_5)_3$		159	0.9207	1.3853	(5, 9, 88, 91, 92, 203, 276, 277)
$C_2H_5SiCl(OC_2H_5)_2$		151			(203)
$C_2H_5Si(OC_3H_7(n))_3$		203		1.4017^d	(276, 277)
$C_2H_5Si(OC_4H_9(n))_3$		237		1.4128^e	(276, 277)
$C_2H_5Si(OC_4H_9(i))_3$		102 (8 mm.)			(139)
$C_2H_5Si(OC_5H_{11}(n))_3$		285	0.891	1.4210^d	(276)
$C_2H_5Si(OC_5H_{11}(i))_3$		153 (17 mm.)			(139, 276)
$n\text{-}C_3H_7Si(OC_2H_5)_3$		180	0.852	1.4076	(249, 276)
$i\text{-}C_3H_7Si(OC_2H_5)_3$		178	0.9194		(9)
$CH_2{=}CHCH_2Si(OC_2H_5)_3$		175	0.9229	1.3952	(9, 10)
$n\text{-}C_4H_9Si(OC_2H_5)_3$		191	0.895^h	1.3976^i	(276, 278)
$i\text{-}C_4H_9Si(OC_2H_5)_3$		186	0.9104	1.3908	(5, 9)
$(i\text{-}C_4H_9)SiCl(OCH_3)(OC_2H_5)$		155			(178)
$i\text{-}C_5H_{11}Si(OC_2H_5)_3$		198	0.8955	1.3982	(9, 249)
$n\text{-}C_6H_{13}Si(OC_2H_5)_3$		210	0.8938	1.4167	(9)
$(C_6H_{11})_2(C_6H_5)Si(OC_6H_{11})$	103–4	200 (0.5 mm.)			(52)
$(C_6H_5)_2Si(OC_2H_5)_2$		303			(180)
$(C_6H_5)_2Si(OC_2H_4Cl)_2$		144 (0.1 mm.)	1.2027^b	1.5510^a	(312)
$(C_6H_5)_2Si(OC_6H_5)_2$	70–1				(167, 181)
$(C_6H_5)_2Si(OC_6H_5)Cl$		253 (40 mm.)			(167)
$C_6H_5Si(OC_2H_5)_3$		233	1.0133^c		(145, 204, 207, 231, 276)

TABLE 6—*Concluded*

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$C_6H_5Si(OC_2H_4Cl)_3$		158 (1 mm.)	1.2680^b	1.5077^a	(262, 312)
$C_6H_5Si(OC_3H_7(n))_3$		192 (7 mm.)	1.036^b	1.5025^a	(276)
$C_6H_5Si(OC_4H_9(i))_3$		156 (10 mm.)			(139)
$C_6H_5Si(OC_5H_{11}(i))_3$		196 (18 mm.)			(139)
$C_6H_5Si(OC_6H_5)_3$	40	250 (13 mm.)			(138)
$(C_6H_5)(p\text{-}BrC_6H_4)Si(OC_2H_5)_2$		201 (17 mm.)	1.2488^b		(106)
$[(C_6H_5)(p\text{-}BrC_6H_4)Si(OC_2H_5)]_2O$		318 (20 mm.)	1.3369^b		(106)
$[C_6H_5Si(OC_2H_5)_2]_2O$		258 (75 mm.)			(231)
$p\text{-}BrC_6H_4Si(OCH_3)_3$		136 (13.5mm.)	1.3493^b		(106)
$p\text{-}BrC_6H_4Si(OC_2H_5)_3$		150 (12 mm.)	1.2244^b		(106)
$p\text{-}BrC_6H_4Si(OC_3H_7(n))_3$		176 (14 mm.)	1.1553^b		(106)
$p\text{-}BrC_6H_4Si(OC_4H_9(i))_3$		191 (14 mm.)	1.0923^b		(106)
$p\text{-}NH_2C_6H_4Si(OC_2H_5)_3$		148 (14 mm.)			(76)
$p\text{-}(CH_3)_2NC_6H_4Si(OC_2H_5)_3$		181 (14 mm.)			(76)
$C_6H_5CH_2Si(OC_2H_5)_3$		248	0.9864		(249)
$C_6H_5C{\equiv}CSi(OC_2H_5)_3$		142 (6 mm.)	0.986^j	1.4898^k	(355)
$(C_6H_5C{\equiv}C)_2Si(OC_2H_5)_2$		185 (12 mm.)	1.0001^l	1.529^m	(355)
$2,4\text{-}(CH_3)_2C_6H_3Si(OC_2H_5)_3$		270			(145)
$\alpha\text{-}C_{10}H_7Si(OC_2H_5)_3$		294			(143, 144, 145, 249)
$\beta\text{-}C_{10}H_7Si(OC_2H_5)_3$		272			(145)

a, n_D^{20}; b, d_4^{20}; c, d^0; d, n_D^{22}; e, n_D^{24}; f, d^{23}; g, d^{24}; h, d_4^{29}; i, n_D^{29}; j, d_{22}^{22}; k, n_D^{21}; l, d_9^9; m, n_D^9.

silanes has been discussed in the two preceding sections. It was pointed out that all the silanols are subject to condensation with the elimination of water and the formation of siloxanes, and that the rate of condensation depended upon the size and number of the organic groups as well as on the external factors of temperature and catalysts.

Those organosilanols which are sufficiently stable to permit isolation are listed in table 7. Some of these, like triethylsilanol, may be distilled without appreciable condensation (200, 203, 307); others, like diphenylsilanediol, may be purified by crystallization in inert solvents. The ready condensation of diphenylsilanediol in solution by strong acids and alkalies offers a remarkable example of specific catalysis (35).

Besides the simple organosilanols of the type $R_nSi(OH)_{4-n}$ there are listed some α,ω-siloxanediols with siloxane chains of varying length. These are prepared by the hydrolysis of α,ω-dichlorosilanes, which in turn are obtained by the partial hydrolysis and condensation of dialkyldichlorosilanes (35). It remains doubtful whether such a chain can be extended by the reaction of the terminal hydroxyl group with fresh dichlorosilane to split out hydrogen chloride and add a siloxane unit. These α,ω-siloxanediols may also be prepared by careful fractionation of hydrolysis products of the dichlorosilane and by reaction of a cyclic siloxane with water (157, 160, 184, 185, 283, 284, 285, 286, 287, 288).

TABLE 7

Organosilanols—including polymeric diols

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$(CH_3)_3SiOH$		100	0.8112[a]	1.3880[b]	(307)
$(CH_3)_2(Cl_2CH)SiOH$		89 (40 mm.)			(198a)
$(CH_3)(C_2H_5)(C_6H_5)SiOH$		115 (17 mm.)			(175, 176)
$(CH_3)(C_6H_5CH_2)_2SiOH$		241 (60 mm.)			(176)
$(C_2H_5)_3SiOH$		153.5	0.8647[a]		(106, 200, 203)
$(C_2H_5)_2Si(OH)_2$	96	140 dec.			(57, 58)
$(C_2H_5)_2(C_6H_5)SiOH$		165 (60 mm.)			(176)
$(C_2H_5)_2(C_6H_5CH_2)SiOH$		165 (40 mm.)			(175, 176)
$(C_2H_5)(n\text{-}C_3H_7)(C_6H_5)SiOH$		250			(150)
$(C_2H_5)(n\text{-}C_3H_7)(C_6H_5CH_2)\text{-}SiOH$		155 (25 mm.)			(147, 151, 175, 176, 223)
$(C_2H_5)(i\text{-}C_4H_9)(C_6H_5CH_2)\text{-}SiOH$		163 (25 mm.)			(215)
$(C_2H_5)(C_6H_5)Si(OH)_2$	70				(283, 286)
$(C_2H_5)(C_6H_5CH_2)_2SiOH$	54				(282)
$(C_2H_5)(C_6H_5CH_2)Si(OH)_2$	100				(283, 286)
$HO[Si(C_2H_5)(C_6H_5)O]_2H$	87.5				(283, 286)
$(n\text{-}C_3H_7)_3SiOH$		207			(257, 258)
$(n\text{-}C_3H_7)_2Si(OH)_2$	100				(57)
$(n\text{-}C_4H_9)_2Si(OH)_2$	97				(57)
$(i\text{-}C_5H_{11})_3SiOH$		270			(351)
$(C_6H_{11})(C_6H_5)Si(OH)_2$	123–4 dec.				(51)
$(C_6H_{11})_2(C_6H_5)SiOH$	145–6				(51)
$(C_6H_5)_3SiOH$	155			1.1777	(63, 136, 175, 177, 208, 223, 319)
$(C_6H_5)_2Si(OH)_2$	132; 148; 155				(35, 138, 156, 159, 185, 224, 353)
$(C_6H_5)(C_6H_5CH_2)Si(OH)_2$	106				(224, 283, 286)
$HO[Si(C_6H_5)_2O]_2H$	113–4				(35, 157, 160, 185)
$HO[Si(C_6H_5)_2O]_3H$	111–2				(35, 157, 160, 184, 185)
$HO[Si(C_6H_5)_2O]_4H$	128.5				(184, 185)
$(C_6H_5CH_2)_3SiOH$	106				(62, 136, 175, 282)
$(C_6H_5CH_2)_2Si(OH)_2$	101				(62, 282, 284, 285)
$HO[Si(C_6H_5CH_2)_2O]_2H$	76				(284, 288)
$HO[Si(C_6H_5CH_2)_2O]_3H$	82				(287, 288)
$(p\text{-}CH_3C_6H_4)_3SiOH$	99–100				(340)
$(p\text{-}CH_3C_6H_4)_2Si(OH)_2$	113–6				(271)

a, d_4^{20}; b, n_D^{20}.

The silanols, R_3SiOH, where the R's may be all the same or different, are also prepared by reaction of $[R_2SiO]_x$ with the desired Grignard reagent and subsequent hydrolysis of the addition product (175, 176).

Silanol hydroxyl groups in general will react with methylmagnesium iodide to liberate methane, and this reaction is used as a method of determining hydroxyl groups in complex siloxane structures (307).

G. ESTERS, $CH_3COOSiR_3$ AND $(R_3SiO)_2SO_2$

The esters of the organosilanols are formed by the interaction of the silanol with either inorganic or organic acids or their anhydrides. These compounds differ from the ethers or alkoxysilanes in that the silanol has behaved as an alcohol rather than as a silicic acid; hence an acid radical replaces the alkoxy or aroxy radical found in the ethers. In general, the formation of these compounds is carried out by reaction of an acid with the halogenosilane or by interchange of an acid anhydride with an alkoxysilane or siloxane. The following reactions will illustrate the methods which have been used:

(1) $R_3SiOR' + (CH_3CO)_2O = R_3SiOCOCH_3 + R'OCOCH_3$
(2) $R_3SiX + AgOCOCH_3 = R_3SiOCOCH_3 + AgX$
(3) $R_3SiOH + CH_3COCl = R_3SiOCOCH_3 + HCl$
(4) $2R_3SiX + H_2SO_4 = (R_3Si)_2SO_4 + 2HX$
(5) $(R_3Si)_2O + SO_3 = (R_3Si)_2SO_4$
(6) $3(R_3Si)_2O + P_2O_5 = 2(R_3Si)_3PO_4$

The resulting esters, together with their properties and the pertinent references, are given in table 8.

H. THE LINEAR AND CYCLIC ORGANOSILOXANES

The molecular condensation of silanols to siloxanes becomes a very important reaction by which the organosiloxane polymers are formed in practice. However, it should not be concluded that intermolecular condensation is the only mechanism by which such siloxanes may be formed. The preparation of ethyl silicone by the oxidation of tetraethylsilane (290a, p. 73) takes place without benefit of intermediate silicols, and of course the formation of silicon dioxide by the burning of silicon in dry oxygen is the ultimate example of the formation of siloxane linkages without condensation. Most unoxidized compounds of silicon are driven to seek the oxidized forms by the thermodynamic drive of a high heat of oxidation, and hence will move in that direction when the conditions are appropriate.

The name *siloxane* is derived from the names for a series of hydrides in which the silicon atoms are separated by oxygen, as in disiloxane, $H_3SiOSiH_3$. If the hydrogen atoms were fully substituted, we would have an organodisiloxane of the type $R_3SiOSiR_3$. If prosiloxane, $(H_2SiO)_x$, should undergo similar substitution, the product would be a polyorganosiloxane, $(R_2SiO)_x$. Such a substance could be prepared by condensation of a corresponding diol, $R_2Si(OH)_2$, in which case the siloxane chains would have terminal hydroxyl groups and therefore could undergo further condensation with similar molecules or with uncondensed diols. The length of the siloxane chain of the type —$R_2SiOR_2SiOR_2SiO$— therefore would be limited only by conditions which inhibit or do not adequately encourage condensation of the terminal hydroxyl groups.

Since a growing siloxane chain may become long enough for its two terminal hydroxyl groups to condense, there is a possibility that it will go over to a cyclic anhydride. Such a cyclic substance could not then undergo further reaction or rearrangement unless means were provided for the opening of siloxane bonds. For this reason the cyclic siloxanes of the type $(R_2SiO)_x$ are relatively stable substances with vapor pressures that decrease regularly as the value of x increases. No evidence for a cyclic dimer has been reported, but cyclic configurations from trimer to nonomer are known (114, 115, 266, 365). Usually both cyclic and linear types are obtained from the condensation of a given silanediol, but the proportions of each are variable over wide limits depending upon the conditions used.

TABLE 8

Esters

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$[(CH_3)_3Si]_2SO_4$	45–6				(266)
	56–8				(333)
$[(C_2H_5)_3Si]_2SO_4$		170 (12 mm.)		1.4442^a	(333)
$[(CH_3)_3Si]_3PO_4$		86 (4 mm.)		1.4090^a	(308)
$(CH_3)_3SiOCOCH_3$		103			(312)
$(C_2H_5)_3SiOCOCH_3$		168	0.9039^b		(201, 203)
$(C_2H_5)Si(OC_2H_5)_2(OCOCH_3)$		191.5	1.020^c	1.4048^a	(277)
$(n\text{-}C_3H_7)_3SiOCOCH_3$		214			(257, 258)
$(C_6H_5)_3SiOCOCH_3$	91.5				(177, 178)

a, n_D^{20}; b, d^0; c, d_4^{20}

Cyclic dimethylsiloxanes obtained by the hydrolysis of dichlorodimethylsilane have been separated from the linear dimethylsiloxanes and isolated from each other by fractional distillation (114, 266), the total yield of cyclic forms constituting approximately 50 per cent of the hydrolyzate. The remaining linear siloxanes may then be converted quite completely into cyclic forms by heating to 350°C. or 400°C. in the absence of oxygen, at which temperatures the siloxane bonds rearrange and the volatile cyclosiloxanes distil off as they form. The pyrolysis of dimethylsiloxanes apparently takes place without rupture of the methyl-silicon bond, and therefore is a "clean" reaction which leaves no residue (266, 322). Conversion of cyclic to linear dimethylsiloxanes requires low-temperature rearrangement by reagents capable of opening the siloxane bonds of the cyclic molecule, and recombination of the fragments in linear form (266).

Properties of the organosiloxanes and references to the pertinent articles are given in table 9.

TABLE 9

Organosiloxanes

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$CH_3[(CH_3)_2SiO]_1Si(CH_3)_3$		100.5	0.7619^a	1.3774^b	(53, 115, 307, 365)
$CH_3[(CH_3)_2SiO]_2Si(CH_3)_3$	*ca.* −80	153	0.8200^a	1.3848^b	(115, 266, 365)
$CH_3[(CH_3)_2SiO]_3Si(CH_3)_3$	*ca.* −70	194	0.8536^a	1.3895^b	(115, 266, 365)
$CH_3[(CH_3)_2SiO]_4Si(CH_3)_3$	*ca.* −80	229	0.8755^a	1.3925^b	(115, 266, 365)
$CH_3[(CH_3)_2SiO]_5Si(CH_3)_3$	< −100	142 (20 mm.)	0.8910^a	1.3948^b	(115, 266, 365)
$CH_3[(CH_3)_2SiO]_6Si(CH_3)_3$		184.5 (40 mm.)	0.911	1.3965	(365)
$CH_3[(CH_3)_2SiO]_7Si(CH_3)_3$		202 (39.3 mm.)	0.913	1.3970	(365)
$CH_3[(CH_3)_2SiO]_8Si(CH_3)_3$		199 (16 mm.)	0.918	1.3980	(365)
$CH_3[(CH_3)_2SiO]_9Si(CH_3)_3$		203 (10 mm.)	0.925	1.3988	(365)
$CH_3[(CH_3)_2SiO]_{10}Si(CH_3)_3$		202 (4.7 mm.)	0.930	1.3994	(365)
$[(ClCH_2)(CH_3)_2Si]_2O$		204.5	1.045^a	1.4390^b	(198)
$(ClCH_2)(CH_3)_2SiOSi(CH_3)_3$		151.7	0.9105^a	1.4106^b	(198)
$[(CH_3)_2(CHCl_2)Si]_2O$		150 (40 mm.)	1.2213^a	1.4660^b	(198a
$[(CH_3)(C_6H_5)_2Si]_2O$	51-2				(165)
$[(CH_3)(C_6H_5CH_2)_2Si]_2O$	56				(175)
$[(CH_3)_3SiO]_3SiCH_3$	*ca.* −80	190	0.8497^a	1.3880^b	(115, 266)
$[(CH_3)_2SiO]_3$	64	134			(114, 128, 266, 365)
$[(CH_3)_2SiO]_4$	17.5	175	0.9558^a	1.3968^b	(114, 115, 266, 365)
$[(CH_3)_2SiO]_5$	−38	210	0.9593^a	1.3982^b	(114, 115, 266, 365)
$[(CH_3)_2SiO]_6$	−3	245	0.9672^a	1.4015^b	(114, 115, 266, 365)
$[(CH_3)_2SiO]_7$	−26	154 (20 mm.)	0.9730^a	1.4040^b	(114, 115, 266, 365)
$[(CH_3)_2SiO]_8$	31.5	175 (20 mm.)		1.4060^b	(80, 114, 266, 365)
$[(CH_3)_2SiO]_9$		*ca.* 188 (20 mm.)		1.4070^b	(266)
$[(CH_3)_2SiO]_3[(ClCH_2)$-$(CH_3)SiO]$	−1	214	1.0444^a	1.4158^b	(198a)
$(CH_3)_8Si_5O_6$	118	203			(322)
$(CH_3)_{10}Si_6O_7$	51	232			(322)
$(CH_3)_8Si_6O_8$	119	220			(322)
$(CH_3)_{10}Si_7O_9$	150	248			(322)
$(CH_3)_{10}Si_8O_{11}$	139	257			(322)
$(CH_3SiO_{1.5})_n$	Sublimes	without melting			(322)
$(CH_3)_8Si_5O_6$	121	204			(322)
$(CH_3)_{10}Si_6O_7$	57	230			(322)
$(CH_3)_{12}Si_7O_8$	31	254	1.0352^c	1.4031^d	(322)
$(CH_3)_{14}Si_8O_9$	−12	157 (20 mm.)	1.0260^a	1.4032^b	(322)

TABLE 9—*Concluded*

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$[(C_2H_5)_3Si]_2O$		231	0.8590	41.430^b	(58a, 87, 89, 193, 203)
$[(C_2H_5)(n\text{-}C_3H_7)(C_6H_5\text{-}CH_2)Si]_2O$		246 (20 mm.)			(161, 223)
$[(C_2H_5)(i\text{-}C_4H_9)(C_6H_5\text{-}CH_2)Si]_2O$		251 (25 mm.)			(215)
$[(C_2H_5)(C_6H_5)_2Si]_2O$	65.5				(222, 223)
$[(C_2H_5)(C_6H_5CH_2)_2Si]_2O$	55				(282)
$[(C_2H_5)(C_6H_5)SiO]_3$	177.5				(128)
$[(C_2H_5)(C_6H_5CH_2)SiO]_3$		310 (22 mm.)			(282)
$[(n\text{-}C_3H_7)_3Si]_2O$		285			(258)
$[(i\text{-}C_5H_{11})_3Si]_2O$		365			(351)
$[(C_6H_{11})_2SiO]_3$	237–9				(51)
$[(C_6H_{11})(C_6H_5)SiO]_3$	117–8				(51)
$[(C_6H_5)_3Si]_2O$	222				(177, 178, 319, 320)
$[(C_6H_5CH_2)_3Si]_2O$	205				(75, 231)
$[(p\text{-}CH_3C_6H_4)_3Si]_2O$	223–4				(340)
$[(C_6H_5)_2SiO]_3$	190	295 (1 mm.)			(35, 62, 122, 157, 160, 185, 357)
$[(C_6H_5)_2SiO]_4$	201 188	335 (1 mm.)	1.185^e		(35, 36, 122, 157, 160, 184, 185)
$[(C_6H_5CH_2)_2SiO]_3$	98				(288, 357)
$[(p\text{-}CH_3C_6H_4)_2SiO]_3$	261–2				(271)

a, d_4^{20}; b, n_D^{20}; c, d_4^{20} of supercooled liquid; d, n_D^{20} of supercooled liquid; e, density of crystals.

See also alkoxysiloxanes, α,ω-siloxanediols, α,ω-dichlorosiloxanes, and organopolysilanes in their respective tables.

I. SILAZANES AND RELATED COMPOUNDS

Ammonia reacts with silicon tetrachloride first to form a hexaammonate and then to replace the four chlorine atoms with amino groups (290a, p. 10). A similar reaction occurs with all of the chlorosilanes, and provides a method for the preparation of silazanes and other substances having silicon–nitrogen bonds. For example, two molecules of chlorotrimethylsilane condense with one molecule of ammonia to form hexamethyldisilazane (307):

$$2(CH_3)_3SiCl + 3NH_3 = (CH_3)_3SiNHSi(CH_3)_3 + 2NH_4Cl$$

This process is seen to be analogous to that of hydrolysis of the chlorotrimethylsilane, followed by condensation of the silanol. A similar reaction with dichlorosilanes or trichlorosilanes opens the possibility of preparing many polymeric substances which are the nitrogen equivalents of the organopolysiloxanes or silicones. However, the possible utility of such substances is impaired by the fact that the silicon–nitrogen bond is quite readily hydrolyzed to regenerate ammonia and form a corresponding siloxane.

The successful attachment of three trimethylsilyl groups to nitrogen has not been reported. Two such groups may be attached quite readily, but there appears to be a hindrance to the reaction of a third (311). Primary and secondary amines also react with chlorosilanes to form silicon–nitrogen bonds, and this reaction provides a method for making silylamines having various organic groups linked directly to nitrogen (311). Examples of such compounds are given in table 10, along with the known silazanes and their physical constants.

TABLE 10

Silazanes

COMPOUND	MELTING POINT	BOILING POINT	d	n_D	REFERENCES
	°C.	°C.			
$(CH_3)_3SiNHCH_3$		71	0.7395[a]	1.3905[b]	(311)
$(CH_3)_3SiNHC_2H_5$		90.5		1.3912[b]	(311)
$(CH_3)_3SiN(C_2H_5)_2$		126.3		1.4112[b]	(311)
$[(CH_3)_3Si]_2NH$		126.2	0.7741[a]	1.4078[b]	(307, 311)
$[(CH_3)_3Si]_2NCH_3$		145			(311)
$(C_2H_5)_3SiNH_2$		137.3		1.4259[b]	(311, 329)
$(C_2H_5)_3SiNHC_2H_5$					(193)
$[(C_2H_5)_3Si]_2NH$					(193)
$(C_2H_5)_2(CH_2CHCl)SiNH_2$		93 (38 mm.)		1.4570[b]	(329)
$(C_2H_5)(n\text{-}C_3H_7)(C_6H_5)SiNHC_6H_4CH_3$					(150)
$(n\text{-}C_3H_7)_3SiNH_2$		189		1.4359[b]	(329)
$(C_6H_5)_3SiNH_2$	55–6				(194)
$[(C_6H_5)_3Si]_2NH$	175				(281)
$(C_6H_5)_3Si\cdot C_2H_5NH_2$	45				(192)

a, d_4^{20}; b, n_D^{20}.

V. THE SILICONE POLYMERS

As has been shown above, the partial oxidation of an organosilane or the condensation of an organosilanol will yield an organosiloxane. If there are three organic groups and one hydroxyl group on each silicon atom, the molecule is seen to be monofunctional and hence may condense with only one similar molecule to produce an organodisiloxane (307). If each silicon atom bears two organic groups and two hydroxyl groups, the molecule becomes bifunctional and is capable of forming straight-chain siloxanes which are multiples of the unit structure $[R_2SiO]$. Such polymeric siloxanes may reach a very high molecular weight, being limited only by cyclization or by the attachment of chain-terminating groups that block further reaction (123, 128, 266). In like manner, the silicon atom which bears one organic substituent and three hydroxyl groups becomes trifunctional and is capable not only of propagating a siloxane chain but also of forming an oxygen bridge or cross link to a similar trifunctional unit in a neighboring chain (301). Silicic acid, which may be considered to exist momentarily during the hydrolysis of silicon tetrachloride, is tetrafunctional and so may form two corresponding links to neighboring structures (290).

With mono-, di-, tri-, and tetra-functional units available, it is seen that a wide variety of siloxane chains may be built, and that the various types may have properties which depend upon the degree of cross linking as well as the nature of the organic groups which are attached to silicon. The name *silicone* was given to substances of the empirical formula R_2SiO by Kipping (158), because he thought they were analogous to the ketones, but he was the first to recognize that these substances are in fact polymeric and show no resemblance, chemical or otherwise, to the organic ketones. Kipping also recognized that the silicones became polymeric through a process of intermolecular condensation (244, 245), and he was able to isolate several of the lower-molecular-weight polymers as well as some of the intermediate condensation products to prove his point. The name *silicone*, instead of dropping out of usage as an inept analogy, has persisted and has become a generic term for all polymeric organosiloxanes (306), even though they may be cross linked and so contain an average of less than two organic groups per silicon atom. For this reason it has been necessary to name pure compounds as individual siloxanes and to use the word silicone only to denote a general type of organopolysiloxane.

Only a few general types of alkyl and aryl silicones need be considered here, for a detailed description of the useful polymers is more properly the function of the technical literature.

In the alkyl series the first and perhaps the best-known organopolysiloxane is methyl silicone (291, 301). This may take the form of an oil (266, 365), elastomer (16, 368), or a resinous substance (301), depending upon the molecular size, the degree of cross linking, and (to some extent) the method of manufacture. Of the various types of polymer, the simplest from the point of structure is the oil, which is composed of the linear polymethylsiloxanes shown in table 8 and their longer-chain homologs. As the average number of siloxane units in the chain increases, the resulting oil becomes more viscous, less volatile, and of somewhat higher melting point. The physical chemistry of the series up to the linear decamer has been studied very thoroughly (114, 115, 266, 365), and it has been found possible to express the vapor pressure and heat of vaporization of any individual compound at a given temperature as a function of the number of siloxane units, according to the following equation:

$$\Delta H_{\text{vap.}}\ \text{linear} = 4.70 + 1.65x\ \text{kg.-cal.}$$

where x is the number of siloxane units in the chain. The activation energy of viscous flow similarly may be expressed as a function of the same variables:

$$E_{\text{vis.}}\ \text{linear} = 1.74 + 1.49 \log x\ \text{kg.-cal.}$$

Expressions for heat of vaporization and energy of flow have been derived in the same way for the equivalent cyclic polymethylsiloxanes, as follows:

$$\Delta H_{\text{vap.}} \text{ cyclic} = 5.45 + 1.35x \text{ kg.-cal.}$$

$$E_{\text{vis.}} \text{ cyclic} = 0.98 + 3.96 \log x \text{ kg.-cal.}$$

The complete comparison shows some interesting differences: for a given number of siloxane units the cyclic compound has a higher viscosity, a greater increase in viscosity with temperature, and a higher vapor pressure than the linear compound.

Among the linear polymethylsiloxanes of higher molecular weight the ratio of energy of vaporization to activation energy of viscous flow approaches a constant value of approximately 3.8; in the cyclic series the same ratio approaches the value of 2.3. The fact that these values become constant with increasing molecular weight is interpreted as meaning that the liquids appear to flow as segments rather than as complete molecules, as was also concluded by Eyring after his investigation of high-molecular-weight hydrocarbons. An interesting comparison may be made between the units of flow in the methyl silicone and the hydrocarbon series (365).

	UNITS OF FLOW	
	Hydrocarbon	Silicone
Composition	$C_{25}H_{50}$	$(CH_3)_{14}Si_7O_7$
Molecular weight	350	519
Volume, Å^3	640	920
E_{vis}	6 to 7 kg.-cal.	3.8 kg.-c

In the silicone oils a smaller amount of energy is capable of opening a hole sufficiently large for the larger unit of flow to pass through. This in turn reflects a smaller attraction between neighboring chains or molecules than is experienced in the hydrocarbon series. Since a very long dimethylsiloxane polymer appears to be encased in hydrocarbon groups when it is set up as a scale model, it is difficult to see why such hydrocarbon-encased chains should not attract each other to about the same extent as do the long hydrocarbon chains themselves.

Silicone oils are noted particularly for their very small change of viscosity with temperature. This property makes the silicone oils more suitable as lubricants, dielectric fluids, and hydraulic fluids under a wide range of temperatures than the hydrocarbon oils. The lower limit of usefulness of the silicone oils extends down to the temperature of solid carbon dioxide. For this reason they have found application at very low temperatures, even though at first they were thought important for their high thermal stability and their resistance to oxidation in service at elevated temperatures (7, 32a, 34, 75a, 111, 142a).

If the molecular weight of a polymeric dimethyl silicone is not limited purposely by the attachment of chain-terminating units, but rather is extended greatly by the action of condensation or rearrangement catalysts, there is produced an elastic gel (368) instead of an oily polymer. This gel, which is properly called an elastomer, may be milled with reinforcing fillers and various curing agents, and then heat treated to produce a so-called silicone rubber. This rubber has the high heat resistance that is characteristic of silicone oils and resins, and retains its rubbery properties at about 100°C. beyond the useful temperature limit of service for natural rubber. It also shows small change of physical properties with temperature, and so remains useful at temperatures as low as −50°C. (290).

The methyl silicone resins are cross-linked polymers with an average of less than two methyl groups per silicon atom. They decrease in density and refractive index, and require a more drastic curing cycle, as the methyl-to-silicon ratio is increased (301). In the range 1.0 to 1.3 methyl groups per silicon atom the resins precipitate readily from solution and cure at moderate temperatures to a hard, rather brittle mass. Resins with CH_3/Si ratios of 1.3 to 1.6 require a temperature of 150–250°C. to harden, but provide a more flexible and durable resin. At higher CH_3/Si ratios the polymer constituents may become volatile before their molecular weight has been sufficiently increased by condensation. Those resins in the stated ranges find application as laminating resins, as insulating materials, and in protective coatings (55, 290, 291, 298, 310, 367).

Ethyl silicone resins (6, 119, 124, 125, 126, 128, 233) differ from the methyl in being softer, more flexible, and slower to condense for a given ratio of organic groups to silicon atoms. For this reason, a smaller proportion of ethyl groups suffices to produce a resin with physical properties similar to those of a given methyl silicone resin. The higher alkyl silicone resins become progressively softer and more readily oxidized as the alkyl chains are lengthened; they do not have the thermal stability and chemical inertness which are important advantages to the methyl silicones, and hence are not as interesting in a practical way. Higher trichlorosilanes of the type $RSiCl_3$, in which R represents an alkyl group of five or more carbon atoms, hydrolyze to soluble resinous substances instead of to the insoluble white powders ("siliconic acids") which are formed upon hydrolysis of the lower alkyl trichlorosilanes. Similarly, benzyltrichlorosilane hydrolyzes to a soluble resinous condensation product which may further be condensed to an insoluble resin (231, 249). The corresponding cyclohexyl compound forms polymeric compounds which were described by Kipping as "gluelike" in consistency (256).

Some marked contrasts are encountered in the series of aryl silicones. Diphenylsilanediol is a rather stable white crystalline substance which begins to condense to phenyl silicone only at its melting point (148°C.) or higher. However, it too responds to the action of condensing agents (35, 159); if the crystals of the diol are dissolved in ether and treated with a small amount of concentrated hydrochloric acid, the cyclic trimer of phenyl silicone (hexaphenylcyclotrisiloxane) is formed almost exclusively, but if the diol is dissolved in boiling alcohol and a small amount of strong caustic is added, crystals of the cyclic tetramer (octaphenylcyclotetrasiloxane) are formed with little or no trimer. Crystals of the trimer may also be converted to the tetramer by dissolving them and adding a few drops of strong alkali, so it must be concluded that the specificity of acids and alkalies as catalysts is concerned with their ability to rearrange siloxane bonds as well as their influence upon the condensation of hydroxyl groups.

Diphenyl silicone of high molecular weight is a brittle rosin-like substance with a melting point that continues to rise with further condensation. These thermoplastic polymers show very high resistance to oxidation, even exceeding that of methyl silicones, but the phenyl groups may be split off by the action of strong mineral acids (128). Chlorination of the phenyl groups (292) (by chlorination of dichlorodiphenylsilane before hydrolysis) produces a similar brittle sticky resin which does not burn if the number of chlorine atoms is almost equal to the number of hydrogen atoms in each phenyl nucleus.

The xylyl, naphthyl, and higher aryl silicones (207, 231, 245, 341) also are thermoplastic, brittle, and sticky. A phenoxyphenyl silicone of this type, with high thermal stability, has been reported (294).

By introducing both alkyl and aryl groups into an organosiloxane polymer, an increase in physical strength and toughness may be obtained. For example, some popular compositions for insulating and protective resins are methyl phenyl silicones in which the molar proportion of phenyl to methyl may be anywhere from 1:10 through 1:1. Such methyl phenyl silicone resins (26, 295, 336) may be made either by the hydrolysis and condensation of methylphenyldichlorosilane, or by the hydrolysis of a suitable mixture of methyl- and phenyl-chlorosilanes, followed by intermolecular condensation of the hydrolysis products to get a random distribution of methyl and phenyl silicone units in the polymer. Various degrees of cross-linking are employed to give the hardness and rate of cure which are required for the application at hand. In these as in all silicone resins the use of rearrangement or condensation catalysts may greatly accelerate the curing process.

Ethyl phenyl silicones (13, 121, 123, 128) may be prepared in much the same manner as methyl phenyl silicone, and are useful as coating compositions and in electrical insulations. Many other mixed alkyl-aryl silicones may be made, and various substituents may be put on the alkyl and aryl groups to make the composition flame-proof or to provide other special properties. Considering the number of usable organic groups, and the number of variations within each group through the use of substituents, it is seen that an almost infinite variety of organosiloxane polymers is possible. Only a few of these have been discussed here, and indeed only a few have been prepared and described in the literature (10b, 14, 16, 22, 33, 49a, 95a, 96, 108a, 113, 140a, 142a, 145a, 191, 211, 251, 251a, 270, 305b, 315a, 359a)

VI. WATER-REPELLENT FILMS

The ability of organosilicon compounds to render certain surfaces water-repellent is a recent discovery (259) in the field. The application depends upon the fact that some organosilicon compounds have a very high contact angle to liquid water (137, 254) and a low solubility in water.

There are three general methods that may be used for applying organosilicon films to surfaces. In the first, organohalogenosilanes are caused to react with hydroxyl groups on the surface to be treated, leaving a film of organosiloxane polymer which is the effective agent in making the surface water-repellent (254, 259, 290, 351a). This reaction may be carried out in the vapor phase if the organosilicon halide is sufficiently volatile to build up an appreciable partial pressure in the treating atmosphere. A mixture of methylchlorosilanes has been especially valuable for use in this way. Reactive silanes which are not sufficiently volatile to be used in the vapor phase may be applied as a solution in an inert solvent, from which an organosiloxane film is deposited by reaction with surface hydroxyl groups as before. Such films deposited by reaction are not removed by organic solvents.

The second general method for applying films makes use of oily dimethylsiloxane polymer which is applied to the surface (preferably in dilute solution) and then heated in air to a temperature of 300°C. or more, whereupon the film becomes chemically attached to the surface and is not thereafter removed by organic solvents (137, 214a). In the third method, suitable varnishes of high water-repellent characteristics are applied to the surface to be treated. Evaporation of the solvent in such a varnish then leaves a film of organosilicon resin which may require further baking or treating to make it durable and effective (255). Films deposited by this method are not chemically bound to the surface and hence have only the usual adhesion of a varnish film.

Some measurements (254) which have been made on water-repellent films deposited by the first method (that is, by the reaction of methylchlorosilanes in the vapor phase with hydroxyl-containing surfaces) are of interest here. These experiments were conducted with steatite, a magnesium silicate composition which is used as a dielectric in high-frequency applications, but presumably the conclusions also apply to films deposited by reaction with any surface having on it a film of absorbed water. It was found that the methylchlorosilane vapor did not produce any water-repellent film on glass which had been dried by heating to 350°C. in vacuum, but would react with glass which had been exposed to room temperature and humidity. The film on steatite was found to be 1.9×10^{-5} cm. thick, and since a scale model of the unit $(CH_3)_2SiO$ shows that its thickness is about 6×10^{-8} cm., the film must be approximately 300 molecules thick. It is known that the absorbed film of water on quartz and on glass is about 100 molecules thick (the actual thickness depending upon the relative humidity of the surrounding air), and therefore it may be concluded that the methylchlorosilane vapor reacts with the absorbed water, molecule for molecule, and replaces it with a corresponding film of organosiloxane polymer. Since the model of a single dimethylsiloxane unit measures about 3 by 7Å., one mole of dimethyldichlorosilane would yield a monomolecular film having an area of 21×10^{-16} sq. cm. $\times$ Avogadro's number, or 1.26×10^9 sq. cm. It is seen that a small amount of chlorosilane vapor is capable of making a considerable surface area water-repellent, and that the actual area so covered will depend upon the actual thickness of the water film which it replaces.

Paper, cotton cloth, wool, leather, wood, and many similar substances may be treated with methylchlorosilane vapor to make them water-repellent, and the film so deposited is not removed by organic solvents or by washing with soap and water. It may be removed only by severe abrasion or by the chemical action of dilute hydrofluoric acid, ammonium bifluoride solutions (24a), or alcoholic sodium hydroxide, reagents which are capable of attacking a siloxane bond (290a, p. 84).

Water-repellent films are applied by the second method to insulators and similar ceramic objects, especially when such objects have metal inserts or coatings which would be damaged by the hydrochloric acid produced during a reaction with chlorosilanes. Apparatus or assembled objects which can neither be heated to high temperature nor be exposed to chlorosilane vapor may be given a water-repellent film by the application of a varnish according to the third method. A suitable varnish for this process contains the methylsiloxane unit, [CH_3SiHO] (255).

VII. SPECIAL INVESTIGATIONS OF PHYSICAL PROPERTIES

Because of its position in the Periodic System, silicon and its compounds are of special interest for comparison with organic compounds and with compounds of the fourth group metals. For this reason some organosilicon compounds have been examined very carefully, not only in order to get good values of melting point, boiling point, and density, but also to determine many less usual properties which relate in some way to the molecular structure of the compounds. The result is an accumulation of excellent measurements on a few of the compounds that happen to be of particular importance.

The crystal structures of dibenzylsilanediol (288), diphenylsilanediol, and the cyclic diphenylsiloxanes have been thoroughly investigated in order to establish the identity of the diol condensation products (36, 122, 185). Tetramethylsilane and the methylchlorosilanes have been investigated by electron diffraction, and have yielded pertinent information on the carbon-silicon and silicon-chlorine bond distances (28, 29, 30, 31, 32, 214). The Raman spectrum of tetramethylsilane is also reported in some detail (4, 279, 326, 358), and calculations have been made for the bond force constants in this compound.

Tetraphenylsilane has been examined thoroughly by crystallographic methods, and an interesting comparison of the fourth group elements (carbon, silicon, germanium, tin, and lead) has resulted from a study of their tetraphenyl compounds (19, 99, 273).

The heat capacity, entropy, and heats of fusion and vaporization for tetramethylsilane have been determined, and there are extensive data on the vapor pressure and heats of vaporization of all the silicon hydrides as well as their alkyl and halogen derivatives (11, 12, 24, 24b–24g, 112, 142, 366). The vapor pressures of the polymeric dimethylsiloxanes have been of interest not only in connection with the uses to which these substances are put, but also for the calculation of heats of vaporization. Precise measurements of viscosity leading to values of the activation energy for viscous flow have allowed comparisons with the energy of vaporization, and from that ratio have come conclusions about the unit of flow in the methylsiloxane polymers (114, 115, 365). The heat capacity of tetraphenylsilane also is known (327).

The isotopic composition of silicon from terrestrial sources and from meteorites has been investigated by preparing alkyl derivatives of silicon from both sources and measuring the densities of these liquids very carefully. The studies have led to the conclusion that the ratio of silicon isotopes is the same in both cases (132, 133, 134, 135).

Measurements of the surface tension and density of several organic derivatives of silicon have given the values of 27.8 for the atomic parachor of silicon (114, 348).

The molar refractions of a large number of organosilicon compounds have been determined (40, 308a), and it is found that the values for the atomic refraction of silicon vary considerably depending upon various substituents on the silicon. It has been suggested that a system of bond refractions, or of bond and group refractions, be substituted for the usual atomic and molecular refractions as a method for determining the purity of compounds or deducing their structure. Given sufficiently reliable data on such bond refractions, it becomes possible to calculate in advance the specific refraction of a compound that is to be prepared.

Since the methylchlorosilanes are made and used in considerable quantity and are quite volatile in nature, it has been necessary to determine the flammability limits of methylchlorosilane vapors in air in order to avoid explosive mixtures during the handling of these substances. It was found (12a) that the lower flammability limit for dichlorodimethylsilane was 3.4 per cent by volume in air, and that for trichloromethylsilane was 7.6 per cent by volume. Combustion of the mixtures with air deposited a very fluffy and finely divided silicon dioxide.

The kinetics of the decomposition of tetramethyl-, tetraethyl-, and tetrapropyl-silanes has been studied (112, 359). The solubility of tetraethylsilane in various solvents is accurately known (21).

Roentgenographic investigations of the structures of methylpolysiloxanes and other organosilicon compounds have been made (80, 136, 371), and data on vapor pressures of chlorotrimethylsilane (349) and ethyl- and phenyl-fluorosilanes (73) have been published.

VIII. ISOMERISM

Organosilicon compounds, like organic compounds, may exist in isomeric forms due to structural or geometrical considerations. Isomerism in the organosilicon compounds can be more complex than that of the similar carbon compounds, owing to the presence of the silicon atoms. In general, the ordinary isomerism that occurs in organic compounds can be manifested in the organic part of the organosilicon compound, but it is in turn made more complex by the presence of the silicon atom.

The structural type of isomerism may occur in the organic radical, occur at the silicon atom, or occur at both. An example of the first type is $n\text{-}C_4H_9SiCl_3$ and $i\text{-}C_4H_9SiCl_3$ (37, 41), while the second type is illustrated by decamethyltetrasiloxane, $(CH_3)_3SiO[(CH_3)_2SiO]_2Si(CH_3)_3$, and 3-trimethylsiloxyheptamethyltrisiloxane, $[(CH_3)_3SiO]_3SiCH_3$ (266). The third type is illustrated by butyltrimethylsilane and triethylmethylsilane (362).

The number of isomers which may occur because of geometrical considerations is more limited, since certain geometrical factors that cause isomerism in carbon compounds have not been observed in organosilicon compounds. No known compounds exist in which silicon is doubly bonded to another atom (165, 315), a fact which would indicate that isomerism of the type existing in compounds such as maleic and fumaric acids does not exist. This type of isomerism can exist, however, in the organic side chain.

Kipping, in his earliest work, was interested in synthesizing organosilicon compounds in which the silicon atom was an asymmetric center. He was able to resolve several of the racemic mixtures he had prepared (46, 47, 147, 148, 149, 150, 151, 152, 153, 161, 174, 215, 216, 223).

IX. Physiological Properties

Ethyl orthosilicate is known to have a hemolytic effect on experimental animals when inhaled or ingested. This effect does not appear to involve any specific action of the silicon, but rather is analogous to the action of ether and the higher alcohols of the red blood cells. The silicic acid or silica formed by hydrolysis of orthosilicates apparently has no physiological response. Methyl silicate shows a specific effect in that the liquid or its vapor seems capable of causing severe irritation or ulceration of the cornea upon actual contact with the eyes (10b). This effect does not seem related to any action of silica or to the action of methyl alcohol upon the optic nerve, and hence it cannot be attributed to hydrolysis products of the methyl silicate. These observations (290a, p. 14) suggest that the substituted alkoxysilanes may have specific physiological effects as solvents or as local irritants, but no such effects have been reported.

The organosilicon halides are capable of hydrolysis on the skin or in the body fluids, and the resulting hydrohalogen acids may be irritating or destructive if they are liberated in sufficient quantity. However, the portion of the molecule containing the carbon–silicon bond does not appear to have any physiological effect. Organosiloxane polymers are bland to the skin and cause no dermatitis; it has not been demonstrated whether they are absorbed in appreciable quantities through the skin, but from their behavior in other circumstances it seems unlikely that even absorbed organosilicon compounds would produce any harmful effects.

The lower alkylfluorosilanes hydrolyze fairly rapidly in moist air and hence exhibit a toxicity due to the hydrolysis product, hydrogen fluoride; butyltrifluorosilane hydrolyzes very slowly and appears to be somewhat toxic *per se*. Inhalation of small quantities of the vapor causes headache and nausea (24e).

The two butylchlorofluorosilanes do not seem to be toxic, save for the action of their hydrolysis products.

The chloromethylsilanes, also being highly volatile, are in danger of being inhaled in quantity during their use. The hydrogen chloride which is liberated by their hydrolysis is irritating; hence all these substances have about the same odor and effect as silicon tetrachloride when inhaled. The products of hydrolysis other than hydrochloric acid undoubtedly are polymethylsiloxanes, and there has been some question as to whether these polymers might accumulate in the lungs upon continued exposure to the vapors. However, x-ray examinations of the lungs of laboratory workers over a period of years have failed to reveal any deposits of silicon-containing material, and it must be concluded that any organosiloxanes so formed are sufficiently soluble in body fluids to be removed. No effect akin to the condition known as silicosis has been experienced.

It may be concluded from these observations that silicon has not been known to cause any specific poisoning analogous to heavy metal poisoning, nor do the organosilicon compounds show any physiological responses that could be attributed to their silicon content or to their carbon–silicon bonds (290a, p. 103).

X. ANALYTICAL METHODS

The traditional methods for determining silicon as silica in natural products involve the ignition or ashing of the sample to recover the silica. Such methods are entirely inapplicable to the analysis of organosilicon compounds, because pyrolysis products or volatile fragments will be lost during the strong heating. It has been necessary to determine silicon by a process of wet oxidation in sealed tubes (274), or by complete combustion in a sealed bomb (352). Wet oxidation with sulfuric (177) and nitric acids in open tubes, or by a Kjeldahl digestion with concentrated sulfuric acid, have been used under precautions to avoid loss of silicon. All these methods give silicon dioxide, which may be weighed as such or may be determined colorimetrically as the blue silicomolybdate (290a, p. 106).

Carbon and hydrogen in organosilicon compounds may be determined by combustion, provided that a sufficiently high temperature is maintained (41). Most organosiloxanes require for their oxidation a temperature considerably higher than that ordinarily used for the combustion of organic compounds. The early investigators used platinum foil or platinized asbestos as filling in their combustion tubes in order to have them function properly at these higher temperatures. With some modification, microcombustion may be used as a more rapid and more convenient method.

By modifying the combustion tube itself so that it may be weighed, it becomes possible to determine carbon, hydrogen, and silicon simultaneously in a single sample (301). The sample is oxidized slowly at a temperature of 200–600°C. in pure oxygen, and the products passed over platinum gauze heated to 800°C. to insure complete combustion. Carbon dioxide and water are collected and weighed as usual, and the silicon dioxide remains within the combustion tube and is weighed as such. Because the combustion tube must be kept small enough to fit in an analytical balance, samples are limited to about 0.05 g. maximum.

Halogen atoms attached to silicon may be determined by hydrolyzing the sample and then determining the halide ion volumetrically, or more conveniently by titrating the hydrohalogen acid which is produced (128; 290a, p. 109). If the halogen is fluorine, alkaline hydrolysis followed by determination of the fluorine by the lead chlorofluoride method is advisable (24b). Any organic halogen which is readily hydrolyzable will be indistinguishable from the halogen attached to silicon.

Non-hydrolyzable organic halogen may be determined by fusion in a Parr bomb, possibly using the same sample that is used for determination of silicon. In halogenosilanes with halogen substituents on the organic groups this method naturally will give only total halogen.

Hydrogen which is present as silane groups will be included in the total hydrogen obtained by combustion, but in many cases it can be determined separately by hydrolyzing the sample in a concentrated solution of sodium hydroxide and measuring the evolved hydrogen (347). Silicon–silicon bonds usually also react with the aqueous alkali and, like the silane hydrogen, will produce one equivalent of hydrogen per silicon–silicon bond (187). It is necessary therefore to know whether both silicon–hydrogen and silicon–silicon are present, and, if so, to determine one independently.

Hydroxyl groups in organosiloxanes may be determined by reaction with methylmagnesium iodide in an apparatus designed to collect and measure the evolved methane (307). Total nitrogen may be determined by a standard Kjeldahl procedure, using concentrated sulfuric acid and a mercury catalyst (41). The same digestion mixture may be used for the determination of the silicon by filtering the silica from the diluted acid before alkali is added for the distillation of the ammonia.

There is an interesting possibility of cleavage of silicones by anhydrous hydrogen fluoride in the presence of a dehydrating agent to give a quantitative yield of organofluorosilanes analogous to the organochlorosilanes from which the silicone originally was prepared (24a).

Specific and molar refractions have been used to confirm the composition of organosilicon compounds. The methyl-to-silicon ratio of the methylpolysiloxanes can be determined from measurements of specific refraction (308a).

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SPECIFIC GROUP REAGENTS FOR PROTEINS

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I. INTRODUCTION

For some time the biological activity of proteins was considered to be due to non-protein moieties such as occur in hemoglobin, cytochrome, the yellow enzyme, etc. When a concerted effort failed to detect in insulin, urease, or pepsin any constituent other than what was regarded as a normal protein component, the hypothesis was accepted that proteins containing only the usual L-amino acids in peptide linkage may possess highly specific biological activities. Investigators next attempted to determine what parts of the protein structure were essential for the various activities. For this purpose a number of reagents were used to modify the proteins. The modified proteins were then assayed and if the activity was found to have been destroyed, it was assumed that the specific group attacked by the reagent played an important rôle in mediating the activity. Since work along these lines is constantly expanding, it appears timely to review the known information concerning the specificity of the various reagents that have been used, and to point out some of the difficulties that may beset an investigator not sufficiently aware of the numerous reactions that may occur.

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It now appears to be clearly established that the amino acid components of proteins are bound together by peptide bonds through their α-amino and α-carboxyl groups and that the rest of the amino acid is essentially free. In the case of the monoaminomonocarboxylic acids, such as alanine, leucine, etc., this is a hydrocarbon chain and is therefore chemically inert. However, the more complicated amino acids possess polar groups or other reactive chemical configurations that are available for chemical reactions. Table 1 contains a list of these groups and of their relative abundance in several typical proteins and in a few of unusual composition.

The number and diversity of protein groups would make a discussion of their chemistry lengthy and involved were it not for the fact that the reactions to be considered will be limited to those that *(1)* do not hydrolyze the peptide bonds or the disulfide groups of the protein backbone, and also, preferably, *(2)* do not cause enough disruption of the original configuration to bring about the drastic, often irreversible, structural changes usually lumped under the term "denaturation." The present review will be concerned only with reactions involving primary bonds on the side chains of proteins. Such reactions may render proteins more resistant or more susceptible to denaturation. When a large proportion of the polar groups have been modified, the question whether the protein has become denatured in the process is often one mainly of terminology, since many of the derivatives have properties usually assigned to denatured proteins (e.g., insolubility at the isoelectric point) and yet resemble native proteins in other respects. It should be noted that proteins vary greatly in their sensitivity to various types of denaturing agents and that, therefore, the conditions suitable for the preparation of "native derivatives" of one protein may cause denaturation of another.

Many protein derivatives have been found to be as homogeneous as the protein from which they were prepared (for examples, see 65, 87, 154, 165, 203). These observations indicate that the organic chemical reactions proceed in a straightforward fashion, e.g., a protein molecule in which several of the groups have become substituted is not then more reactive than is the original protein. If, for example, 60 acetyl groups have been introduced, any individual molecule may be expected to contain a number somewhere in the range of 55 to 65 rather than in the range of 20 to 100 introduced groups. On a statistical basis also, it would be expected that derivatives would be homogeneous whenever an appreciable number of protein groups have participated in the reaction. This homogeneity makes possible the assignment of biological activity to a derivative, and not necessarily to small amounts of unreacted protein in the product obtained after reaction.

If inhomogeneous derivatives are obtained, it appears probable that denaturation changes may have intervened. For reasons not yet thoroughly understood, part of the groups in some native proteins do not appear to be available for reaction but can be made to become so by "denaturation." This phenomenon has recently been reviewed in detail (249). The disruption of the highly organized protein molecule "unmasks," physically or chemically, groups that could not otherwise be detected. Differences in availability have been demonstrated for sulfhydryl, disulfide, and tyrosine groups (reviewed in 10 and 249; see also 200). The possibility that other polar groups may similarly be made more reactive by denaturation has been suggested (10).

Main emphasis will, in this review, be placed on specific protein reagents. These are reagents which under suitable conditions affect only one type of group. A recent comprehensive review of the reactions of native proteins (166) makes unnecessary the inclusion of details concerning many non-specific reagents.[2] Also, since the older literature dealing with the chemical reactions of proteins contains little data of assistance in determining the nature of the reactions observed, it has not been considered in detail. Literature references are available (1, 90, 196).

Criteria for specific reagents

The ideal reagent for the determination of a group specificity should meet the following criteria:

1. The amount of reagent introduced or used up should be measurable.
2. The protein group to be reacted should be measurable.
3. The amount of reagent introduced or used up should be equivalent to the number of protein groups that have reacted.
4. The reaction should proceed under mild conditions and, preferably, be reversible by mild treatment.

If, under these conditions, the biological activity of a purified protein is first lost and then, after reversal of the reaction, regained, the group in question can be said to play a positive rôle in the biological activity.

Such conditions have been met in only a limited number of cases (e.g., 148, 159, 168, 335, 336). More often investigators have used reagents of doubtful claim to specificity, based mainly on the analogy to their reactions with other proteins. However, instances are now known in which reagents do not react in the same manner with different proteins. It would therefore seem to be necessary to check by reliable analytical techniques the effect of each reagent as it is applied to each new protein.

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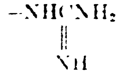
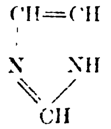
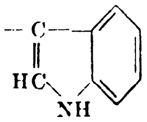
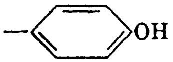
[2] The authors thank Dr. R. M. Herriott for permitting them to see his manuscript (166) prior to publication.

TABLE 1

Reactive groups of proteins

GROUP	STRUCTURE	ORIGIN	RELATIVE ABUNDANCE*						MODEL SUBSTANCE	RELATIVE ABUNDANCE OF DOMINANT GROUP*
			β-Lactoglobulin	Egg albumin	Insulin	Gliadin	Bovine serum albumin	Edestin		
Amino	$-NH_2$	Lysine Peptide chain end	5.8	5.1	5.0	1.0	9.0	1.8		
Guanidyl	 $-NHC(=NH)NH_2$	Arginine	1.6	3.3	1.7	1.5	3.6	9.3	Salmine sulfate	38
Imidazole		Histidine	1.0	1.5	3.3	1.3	2.5	1.9		
Amide	$-CONH_2$	Glutamine Asparagine	7.7	7.4	9.8	32.0	6.2	12.6	Polyglutamine	62
Aliphatic hydroxyl	—OH†	Serine Threonine	8.2	11.1	6.7	6.4	9.7	9.2	Sericin	35
Indole		Tryptophan	1.0	0.7	0	0.3	0.3	0.6	Gramicidin	20
Thiomethyl ..	$-SCH_3$	Methionine	2.2	3.5	0	1.1	0.5	1.6		

Disulfide........	—S—S—	Cystine	1.0	0.4	5.0	1.1	2.2	0.4	Hair	8
Phenol.......		Tyrosine	2.1	2.2	7.0	1.8	3.0	2.4		
Sulfhydryl.....	—SH	Cysteine	0.6	1.0	0	0	0.3	0.25		
Carboxyl .	—COOH	Glutamic acid Aspartic acid Peptide chain end	14.8	10.7	10.0	3.7	12.5	8.4	Polyglutamic acid	78

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* Gram-equivalents per 10^4 gram of protein.

Amino, indole, SH, and carboxyl group analyses are for the most part based on determinations on the intact protein (114). Other groups are calculated from recent amino acid analyses of hydrolysates (52, 64, 218, 263). The values for insulin and β-lactoglobulin are averages. Polyglutamine and polyglutamic acid (110), sericin (266), and gramicidin (110a) analyses are those of this Laboratory. The data are intended to be illustrative of the relative distribution of groups in several proteins rather than of absolute significance. However, it is doubtful that any one figure is more than 20 per cent in error.

† Hydroxyproline and hydroxylysine also furnish aliphatic hydroxyl groups, but these amino acids appear to have limited distribution in proteins.

The attention of investigators has been focused almost exclusively on the sulfhydryl, amino, and phenolic groups of proteins as possible active "centers" for the activities of enzymes, hormones, toxins, and viruses. Neglect of the other polar groups stems in part from the fact that they are less active chemically and thus less likely to be involved in the physiological reactions, but probably is due mostly to the lack of analytical techniques adequate to determine whether or not these groups have reacted with the various reagents.

In Section II of this review we shall outline the present knowledge of the specific reactions available for each of the protein polar groups. In Section III we shall discuss some of the reagents in more detail.

II. Protein Groups

A. SULFHYDRYL GROUPS

The sulfhydryl (hereafter shortened to SH) groups of proteins are attributed to cysteine. Considerably more work has been done with the chemical reactions of this group than with those of the others discussed below, stimulated in part by its essential nature for many enzymes and in part by the intriguing differences in its reactivity in native and denatured proteins. In view of the large numbers of papers in the field and the availability of several comprehensive reviews (10, 31, 157, 158, 219, 295), attention will be directed in this summary only to the most significant recent developments.

Practically all protein reagents react with SH groups. Those that have been claimed to react *only* with this group may be classified as follows: (*1*) mild oxidizing agents (ferricyanide, porphyrindin, iodine, iodosobenzoate, etc.); (*2*) alkylating agents such as iodoacetamide and iodoacetate; and (*3*) mercaptide-forming organometallic compounds such as *p*-chloromercuribenzoate and trivalent organic arsenicals.

The use of oxidizing agents has been criticized (19), since it can be shown that, unless the choice of reagents and conditions is ideal, other protein groups may be attacked. Furthermore, since the primary reversible reaction is a conversion of SH to disulfide bonds, it is dependent upon the spatial proximity of pairs of SH groups.

With iodoacetamide and iodoacetate, the lack of reversibility and lack of specificity are disadvantages (19, 295).

Possibly *p*-chloromercuribenzoate (159) and related mercury and arsenic compounds will prove most helpful in future studies (see Section III,H). The advantages of this class of reagents are: (*1*) they have a great affinity for SH groups and are thus effective under mild conditions and in low concentrations, (*2*) they react with single SH groups, (*3*) they react with SH groups that appear masked to many oxidizing agents, (*4*) they appear highly selective in combining with no protein group other than SH, and (*5*) their combination with SH groups is reversible by the addition of an excess of a simple mercaptan.

The following examples may serve to illustrate the different reactivities of SH groups in proteins to different reagents. Hellermann *et al.* (159) identified the SH groups of *urease* as follows: Assuming a unit weight of 21,300, one SH group was available for reaction with representatives of all three types of reagents (nitroprusside, porphyrindin, iodosobenzoate, chloromercuribenzoate, iodoacetamide) *without* decrease in enzymatic activity. A second SH group reacted rapidly with additional *p*- or *o*-chloromercuribenzoate but was less available to the other reagents mentioned. After this reaction, urease activity was abolished but could be restored by the addition of excess simple SH compounds. Three additional SH groups could be determined in *denatured* urease by means of iodosobenzoate or porphyrindin. Balls and Lineweaver (14, 15) demonstrated that the SH group of *papain* reacted with one equivalent of iodine or iodoacetamide, although it was neither detectable by nitroprusside nor oxidized by porphyrindin. Singer and Barron (296) showed that *p*-chloromercuribenzoate reacted with both free and masked SH groups of a *myosin* preparation to abolish its adenosine triphosphatase activity. On the other hand, porphyrindin or iodosobenzoate oxidized only the free SH groups without causing extensive inactivation. Iodoacetamide, in the low concentrations used, did not react even with the available SH groups.

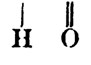
These detailed studies illustrate two points worthy of emphasis: (*1*) There is no clear line of demarcation between "available" and "unavailable" groups; the activities of protein SH groups may vary from that of simple mercaptans to complete resistance to all SH reagents, and (*2*) the activity of a biologically active protein may depend not only on one kind of group, but even only on a single one of several of the same kind occurring in the molecule. This essential group may be more or less chemically reactive, compared to the other similar groups in the molecule.

Such refinement of approach to the general problem of protein group specificity has not yet been achieved for the SH groups of other enzymes, nor for *any* of the other groups of biologically active proteins.

Bersin (30), Hellermann (157, 158), Greenberg and Winnick (139), and Barron and Singer (19, 297) have subjected many enzymes to reaction with SH reagents. With due consideration for variations in rates of reaction and occasional results difficult of interpretation, their data permit valid conclusions to be drawn concerning the essentiality (or lack of essentiality) of the SH groups. Singer (295) has summarized this information.

The importance of SH groups in those proteins that require them for activity tends to overshadow the possible rôles of other groups in the same molecule. To overcome the technical difficulty due to the reactivity of SH groups, Greenberg and Winnick (139) protected the SH groups of papain by oxidation with dilute hydrogen peroxide and then acetylated with ketene. The product was reactivated in the usual manner by reducing agents before assay (see table 2). *p*-Chloromercuribenzoate might be used in similar manner to mask SH groups specifically and reversibly.

Cavallito and Haskell (61) have suggested that the activity of several antibacterial agents may reside in the great reactivity of the structure,



$$CH_2{=}\underset{\displaystyle H}{\underset{|}{C}}{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}$$

TABLE 2

Essentiality of protein groups for biological activity

PROTEIN	PROTEIN GROUPS										REFERENCES
	Amino		Phenol		Sulfhydryl[+]		Other				
	Need	Reagent	Need	Reagent	Need	Reagent	Group	Need	Reagent		
Enzymes:											
Amylase (pancreas)	+	K, F, N, P	−(?)		−	CMB, IA	Disulfide	−	Cy		(210, 211)
											(55)
β-Amylase (barley)	−	K, N	−	N	+	N					(335)
					+	I, CMB, IA, Fe					(336)
Chymotrypsin	−	K, F, N, P	+	K, N	None		Disulfide	−	H₂S		(300)
Lysozyme	+	F, B, P, N			?[a]	I	Carboxyl	+	AA		(5)
							Amide or guanidyl	+	F		(117)
Papain	−	K	+	K	+	Cy, IA[a]					(14, 15)
											(139)
Pepsin	−	K[a]	+	K[a]	None						(162, 173)
			+	I[a]							(163)
	−	N	+	N							(256)
	−	CSO	+	CSO							(323)
Phosphatase (acid)	+	N, F, P									(12)
Phosphatase (alkaline)			+	Oxid.							(299)
	+	K, F, N, P									(137)
Solanain	−	N	+	K, I, N	−	IA, etc.					(139)
Hormones:											
Adrenocorticotropic (pituitary)	+	K, F, N	+	K, I	None						(207)
Gonadotropins:											
Follicle-stimulating (FSH)	+	K, N									(205, 206)
							Disulfide	+	Cy, T		(219)

Interstitial-cell stimulating (ICSH). ..	+	K, N								(205, 206)
							Disulfide	+	Cy, T	(115)
Prolan	−	K[a]	+	K[a]						(205, 206)
	−	N	+	N						(37, 201, 206)
							Disulfide	+	Cy, T	(115)
Hormones:										
Pregnant mare serum (PMS)	+	K, N								(201, 205, 206)
	+	N								(37)
							Disulfide	+	Cy	(95)
	+	A, P								(96)
							Disulfide	+	Cy, T	(115)
Insulin[b]. ...					None		Disulfide	+	Cy	(330)
							Disulfide	+	Cy, T	(341)
			+	I[a]						(148)
							Disulfide	+	T	(311, 337)
							Disulfide	+	$Na-NH_3$	(268)
	−	K[a]	+	K[a]						(312)
	−	K	+	K						(12)
	−	GCT								(179)
							Hydroxyl	−	H_2SO_4	(130)
							Carboxyl	+	AA	(58, 195)
							Amide	−	F	(117)
							Guanidyl	−	F	(117)

TABLE 2—*Continued*

PROTEIN	PROTEIN GROUPS									REFERENCES
	Amino		Phenol		Sulfhydryl[†]		Other			
	Need	Reagent	Need	Reagent	Need	Reagent	Group	Need	Reagent	
Hormones—Continued										
Lactogenic	+	N								(205, 206)
	+	P								(47)
			+	I[a]						(204)
	+	K[a]								(203)
					None		Disulfide[a]	+	Cy, T	(115)
							Carboxyl	+	AA	(202)
Parathyroid							Carboxyl	+	AA	(326)
	+	K[a]								(342)
							Disulfide	−	H_2S, etc.	(325)
							Disulfide	−	Na-NH_3	(269)
Pitocin							Disulfide	−	Cy	(293)
Virus:										
Tobacco mosaic[c]	−	K[a], P[a], N	+?	K[a]						(286, 287)
	−	K[a], P[a]	?	K[a], P[a]						(236)
			+	K	−	I				(11)
	−	B	?	B						(4)
Toxins:										
Diphtheria	+	K[a], F[a]			None					(251)
Scarlet fever	?	K, N	+	I, K, N						(18)
Shiga antigen[d]	+	K								(317)
	+	A								(324)
Crotoxin	+	A	+	I	None		Disulfide	+	Cy	(304)
							Hydroxyl	+	H_2SO_4	(117)
							Carboxyl	+	AA	(117)

[*] *Symbols:*

K = ketene
F = formaldehyde
N = nitrous acid
P = phenyl isocyanate
Cy = cystine or cysteine
CMB = chloromercuribenzoate
IA = iodoacetamide or iodoacetate
Fe = ferricyanide

I = iodine
T = thioglycolate
A = acetic anhydride
GCT = *O*-glucosido-*N*-carbobenzoxytyrosyl azide
AA = acid alcohol
CSO = carbon suboxide
B = benzoyl chloride
Oxid. = oxidizing agents

[a] Analytical data available.

[b] Derivatives of insulin prepared with phenyl isocyanate (175) and carbobenzoxy chloride (128) were inactive, presumptive evidence that amino groups were involved. However, more recent experiments indicate that the phenol groups may have reacted (see text).

[c] Extensive modification of tobacco mosaic virus with carbobenzoxy chloride, chlorobenzoyl chloride, and benzenesulfonyl chloride caused inactivation (236), but the degree of inactivation differed with each derivative depending upon the plant used for the assay.

[d] Both ketene and acetic anhydride may have reacted with the carbohydrate component of the antigen complex.

[e] Although lysozyme can be inactivated by iodine and partially reactivated by reducing agents (5, 227), it has not been possible to demonstrate SH groups by any technique now available (114).

[f] Numerous enzymes have been examined for SH group essentiality. Unless information concerning other groups is available, they have not been included. A table complete to 1945 has been compiled by Singer (295).

for SH groups. It is of interest that maleic acid, proposed by Morgan and Friedman (242) as a SH reagent, has the same basic structure. These investigators indicated that the reaction involved addition to the double bond.

$$\mathrm{RSH} + \mathrm{HOOCCH{=}CHCOOH} \rightarrow \mathrm{RSCH(COOH)CH_2COOH}$$

However, Greenberg and Winnick (139) found that inactivation of SH enzymes by maleic acid was reversible by cysteine and cyanide, and suggested that maleic acid acted as an oxidizing agent.

B. DISULFIDE GROUPS

The only chemical effect of reducing agents on unmodified proteins so far observed is the conversion of disulfide to SH groups. Those most commonly used are cysteine, glutathione, thioglycolic acid, and hydrogen sulfide. The extent and rate of reduction of the disulfide linkage under the same conditions varies for different proteins and is greatly affected by the degree of denaturation (174, 260, 333).

All enzymes that require free SH groups are activated in the presence of low concentrations of reducing agents, which, therefore, do not disturb the basic structure. However, proteins that contain relatively high amounts of cystine appear to be particularly sensitive to, and to be adversely affected by, small amounts of reducing agents. Thus, insulin (12.5 per cent cystine) (233), crotoxin (13.2 per cent cystine) (301), lysozyme (5 per cent cystine) (114), and lactogenic hormone (3.1 per cent cystine) (116) upon reduction become insoluble, possibly through the formation of new hydrogen bonds involving the SH groups. Reduced insulin (18b, 311, 330, 337, 341) and reduced crotoxin (304) are biologically inactive.[3] Miller and Andersson (233, 234) showed that reduced insulin, in the presence of a detergent, had an apparent molecular weight smaller than that of insulin, but that, in the absence of detergent, the reduced insulin was inhomogeneous and highly aggregated.

Conclusions regarding the disulfide groups of other proteins have sometimes been drawn from their biological activities after treatment with reducing agents under the conditions used for inactivating insulin (325). Since it is known that disulfide groups may differ widely in their reactivity toward reducing agents, reinvestigation with adequate analytical controls appears indicated in these cases.

Controlled reduction of the lactogenic hormone by cysteine or thioglycolic acid caused a loss of solubility, but activity could still be demonstrated if suitable means were used for dissolving the reduced protein (116). More severe reducing conditions caused a true loss of activity. Similarly, all types of gonadotropic hormones were inactivated under sufficiently severe conditions of reduction with cysteine or thioglycolic acid (115). However, these hormones are remarkably resistant to reducing agents compared to insulin, which is rapidly inactivated by low concentrations. It seems plausible that drastic reducing conditions would destroy the activity of most biological proteins that contain cystine, including even those enzymes that require one or more free SH groups for activity, but this does not appear to have been demonstrated, although Scott and Sandstrom (292) and Sizer and Tytell (302) showed that increasing concentrations of reducing agents, or decreasing oxidation-reduction potentials, ultimately decreased the activities of papain and urease, respectively. On the other hand, the posterior pituitary hormones (293) and the cobra venom neurotoxin (303) have withstood inactivation by reduction even though they do contain cystine. The extent of reduction was not determined analytically, but in the case of the posterior pituitary hormones, alkylation of the reduced proteins caused inactivation, indicating that the cystine (or cysteine) residues were essential regardless of their being in the oxidized or reduced state.

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[3] The reactivation of reduced insulin by careful oxidation has been reported from one laboratory (see 121), but other workers have been unable to duplicate these experiments (330, 337, 341). If the disulfide linkages of insulin are important structural elements for the integrity of the molecule, it is understandable that reduction would cause internal dislocation. The probability that the correct pairs of SH groups could then recombine during oxidation would be low. However, alternate reduction and oxidation with *retention* of activity might be achieved in the *solid state* with experimental methods similar to those used by Patterson *et al.* (252) with wool.

Considerable attention has been paid to the effect of reducing agents on keratins but the conditions used are more drastic than would usually be applied to bioactive proteins. Several keratins can be dissolved by the use of reducing agents in dilute alkaline media or in neutral solutions of denaturing agents such as urea, guanidine, detergents, etc. (131, 186). The disulfide bonds of wool can be reduced *in situ*, then reacted with bifunctional halogen compounds to form derivatives containing stable bisthioether cross-links (252).

The disulfide bonds of proteins appear to be specifically attacked by two reagents which are often incorrectly regarded as simple reducing agents. Cyanides and sulfites (or bisulfites) add to the disulfide bond to give one SH and one thiocyanate or thiosulfate group, respectively (67, 222). Surprisingly, these agents have proven almost as effective as reducing agents in activating enzymes (32, 139, 340), from which it must be concluded that the unnatural groups thus introduced do not interfere with the specificity of enzymes. In this connection it appears noteworthy that the sulfite-disulfide reaction has been shown to be reversible under mild conditions (41). The nature of enzymes activated by either sulfite or cyanide (or thiosulfate (181)) appears to call for further study.

In alkaline solution protein disulfide bonds are readily hydrolyzed. The lability of the resulting SH and sulfenic acid (—SOH) groups (284) in alkaline solution leads to further complicated changes that have now been studied in detail with wool and hair (77, 209, 239, 285, 315). Lanthionine is one product of the reaction (73, 77, 177). Biologically active proteins rich in cystine, e.g. insulin, are markedly susceptible to the action of alkali (*cf.* 147), but the complexity of the reactions that occur and the possible lability of other types of protein groups under the same conditions have precluded the use of dilute alkali as a specific agent. However, sensitivity of a protein to alkali may suggest that intact disulfide linkages are essential for its activity.

C. AMINO GROUPS

The primary amino groups of proteins are the ε-amino groups of lysine (and hydroxylysine where it occurs) and the α-amino groups at the ends of the peptide chains. In attempting to determine whether amino groups are essential for the activity of proteins, investigators have so far not attempted to differentiate between the two types. In most proteins, the ε-amino groups dominate in number. Insulin is an exception (280).

The availability of three methods for determining amino groups (Van Slyke (327), formol titration (118), ninhydrin color (145)) has made possible correlations between the number of amino groups reacted and the loss of biological activity in those cases where amino groups are essential. The reagents most commonly used to react with the amino groups of proteins have been ketene, nitrous acid, phenyl isocyanate, and formaldehyde. The effects of these reagents will be discussed in detail in Section III. In each case secondary reaction may occur depending upon the conditions used. Fortunately, most investigators have chosen to use two or more of these reagents in studying the essentiality of amino groups (see table 2), and the agreement in results of such multiple experiments appears to be reasonable proof that they may be reliable.

It has recently been observed (114) that acetic anhydride under certain conditions is a highly specific reagent for amino groups. Details are given in Section III. Possibly this reagent will now displace ketene, the use of which has several disadvantages.

Numerous other acylating agents attack the amino group, but these have not been studied in sufficient detail to indicate whether or not they may have useful properties as specific reagents. Mellon *et al.* (226) substituted the amino groups of casein almost exclusively by reaction with very limited amounts of benzoyl chloride. When a slight excess was used, groups other than amino were benzoylated.

Dinitrofluorobenzene has been used to advantage by Sanger to identify the free amino groups of insulin (280) and gramicidin-S (281). The reaction is not specific for amino groups, since the phenol, SH, and, possibly, imidazole groups also react. Its advantage lies in the relative resistance of the introduced bonds to hydrolysis by acid, and in the fact that the dinitrophenyl-substituted products of hydrolysis are colored only if the substituent is on an amino group. These substituted amino acids can be separated and identified by chromatographic techniques.

Since ninhydrin has been used in the determination of amino groups, it appeared likely that it might be a specific reagent for these groups (83, 84, 92). However, the conditions necessary to achieve extensive deamination are quite vigorous, and experiments in this Laboratory indicate that SH and possibly other groups are affected (114).

Several investigators have studied (178, 271, 291) and used (66) the transformation of the amino groups of proteins to guanidyl groups by reaction with *S*-methylisothiourea, or *O*-methylisourea. The possibility that other groups may react has not been investigated in detail but appears to be unlikely. The utilization of this reaction for the modification of biological proteins might be expected to give interesting derivatives.

D. PHENOL GROUPS

The phenolic groups of tyrosine have received considerable attention. Whenever studied, they have been claimed to be essential for activity.[4] The only reagent that has been considered to react *only* with phenolic groups (in proteins containing no SH groups) is iodine. The reaction is one of substitution on the ortho positions (see Section III for conditions used).

Phenolic groups are attacked by acylating agents but usually at slower rates than are the amino groups. Evidence for the extent of reaction has often been based on the color obtained with Folin's phenol reagent (103). Recent observations indicate that such data must be interpreted with caution.[5] The reaction

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[4] Little and Caldwell (210) suggest that the phenol groups of pancreatic amylase are not essential, but the evidence is insufficient to establish the point.

[5] Measurement of protein phenol groups by the Folin phenol reagent has the following disadvantages:

(*1*) The phenol reagent is not specific, since it measures not only phenol, but also indole, SH, and other reducing groups.

(*2*) Tyrosine peptides develop less color than tyrosine (232, 322); hence the color developed by proteins can not be expected to reflect the total tyrosine plus tryptophan contents.

(*3*) Maximal color values are obtained only after proteins are completely denatured (164, 231). This observation suggests that the chromogenic property of tyrosine in the native protein is decreased still further by either hydrogen bonds or steric effects. Actually, the color obtained with proteins varies from 43 to 75 per cent of the calculated values, even lower than the peptide values would suggest (114).

(*4*) The introduction of new groups into a native protein molecule complicates the picture even further, for the new groups may, even without reacting with either phenol or indole groups, so influence their "availability" or their "reactivity" that lower Folin color values are obtained. In one case it has been shown that treatment of tobacco mosaic virus with formaldehyde at pH 7 causes a decrease in this value (188, 275), though neither phenol nor indole groups appear to react under these conditions (108). Furthermore, even where tyrosine groups are acylated, maximal color development depends upon "denaturation" as explained above, and the rates of denaturation differ with different protein derivatives (231).

(*5*) The Folin color cannot quantitatively reflect the extent of reaction of tyrosine residues in proteins when substitution on the carbon atoms of the phenol ring is involved, since all derivatives of tyrosine in which the hydroxyl group is free give some color with the Folin reagent, varying with the kind of groups introduced and the extent of substitution.

Despite these drawbacks, the Folin reaction has been found useful in interpreting the results of ketene acetylation. Herriott (162) developed a method for determining the extent of participation of the phenolic groups in this reaction, based on the observation that phenol acetates are quite unstable in dilute alkali. Even this method cannot be applied indiscriminately to other protein derivatives, since acylated phenol groups differ markedly in their lability toward alkaline hydrolysis (232).

Some of the various disadvantages mentioned above have been overcome in recent work (108) by hydrolyzing protein derivatives by pancreatin (or pepsin) prior to the application of the Folin reagent. By this technique the Folin color with nitrous acid is discussed in detail in Section III. It has been used by Philpot and Small (256) to study the essential nature of the tyrosine groups of pepsin, by Weill and Caldwell (336) with β-amylase, and by others (table 2).

Sizer (301) has claimed that the enzyme, tyrosinase, can oxidize a few tyrosine groups of some proteins, but his conclusions have been questioned (91). The possibility of using enzymes to modify the side chains of intact proteins had not previously been demonstrated, although Harris (150) has since identified a phosphatase in frog's eggs capable of hydrolyzing the phosphate groups of intact phosphoproteins.

Wormall (344) used tetranitromethane as a mild nitrating agent for serum proteins. No chemical studies were made of the derivative, but its similarity in immunological properties to proteins treated with nitric acid is evidence that the phenolic groups were affected. The action of tetranitromethane on simple phenols results in the introduction of nitro groups ortho to the hydroxyl group (283). Further studies of this reagent appear indicated.

Oxidizing agents, when used in excess, attack the phenol (and indole) groups of proteins (6, 299). The ease of oxidation of the phenolic group of tyrosine is enhanced by increases in temperature, pH, and phosphate concentration (49). Herriott (166) has suggested that the Folin reagent might be used to advantage to study the phenol (plus indole) groups of proteins.

The phenolic groups of proteins also react with alkylating agents, diazomethane, diazonium compounds, epoxides, various oxidizing agents, and concentrated sulfuric acid, but not specifically (see Section III).

E. INDOLE GROUPS

Although the indole group is a fairly reactive one, few direct studies have been made concerning its importance in various biological activities. Tryptophan itself reacts readily with a number of reagents, but these reactions are generally dependent upon the free amino group, since acylated derivatives are less reactive.

Lately it has been shown that gramicidin reacts rapidly with formaldehyde in alkaline solution to form a derivative containing methylol (hydroxymethyl) groups on the indole nitrogen atoms (108). The tryptophan residues in typical proteins react similarly, but guanidyl, amino, and amide groups (all absent from gramicidin) also combine with formaldehyde under the same conditions. The introduction of the methylol groups into gramicidin required an alkaline medium and resulted in a loss of toxicity. Since the preparation of formaldehyde toxoids from some toxins also requires, or is favored by, an alkaline medium (82, 88, 97),

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value of untreated proteins has approximated their total tyrosine plus tryptophan contents, and substituents on the phenolic hydroxyl groups can be estimated. Acetylated proteins cannot be analyzed by this technique, owing to the instability of the phenol acetate linkage under the conditions of incubation used.

In contrast to the Folin test, the Lugg and other colorimetric methods are suitable for determining the degree of reaction of the phenolic groups in proteins when substituents stable to acid hydrolysis are introduced in the carbon ring. Even in this case, exceptions exist. Monoiodotyrosine gives an intense Millon test (149, 165). Diodotyrosine gives a positive test by the Thomas procedure (319).

the possibility was expressed that the preparation of some toxoids may involve reactions of the tryptophan residues (108).

The destruction of the indole (and phenol) groups of proteins by oxidizing agents, including the Folin reagent, has already been mentioned. The indole groups of gramicidin are known to be attacked by acylating reagents (110a). In all likelihood, the indole groups of proteins react with nitrous acid and iodine, but the evidence is scattered and requires substantiation (see Section III). In none of these cases would the reaction be likely to be useful in specificity studies.

F. IMIDAZOLE GROUPS

The possible rôle of the imidazole groups of histidine in the biological activities of proteins has received no attention. Of the reagents that are known to react with these groups, diazonium compounds may have promise. Numerous protein derivatives have been prepared by coupling with diazonium compounds (196), but the protein groups involved are not known with certainty. At one time, the reaction was considered to involve only the imidazole and phenol groups, but more recently it has been shown that more of the diazotized compound can be introduced than can be accounted for on the basis of these only (50, 51, 154, 155, 187). The work of Eagle and Vickers (87) suggests that indole and amino groups are also involved. Kapeller-Adler and Boxer (187) believed that coupling occurs with *all* ring compounds, including the pyrrolidine ring.

Histidine gives a strong color upon reaction with diazotized sulfanilic acid (Pauly reaction), the reaction with tyrosine is weaker, and other amino acids do not give colored products (218). It appears possible that the imidazole groups of proteins might be the *only* ones affected by reaction with *limited* amounts of diazo compounds. For example, Reiner and Lang (264) were able to introduce up to 3.8 radicals (per 10^4 gram) of several different diazotized aromatic compounds into insulin without loss of activity and concluded that unsubstituted *phenolic* groups were not essential, in contrast to the results of other investigators (148, 312). However, there are sufficient imidazole residues in insulin (3.3 per 10^4 gram) to account for the added groups (two diazonium molecules may react with each imidazole group). The possibility that limited amounts of diazotized compounds may act as specific reagents for the imidazole ring is worthy of further study.

A number of other reagents are known to attack the imidazole ring, but only under conditions where the reactions of other groups are of first importance. Among these may be mentioned nitrous acid (313, 338), benzoyl chloride (81, 172), and benzenesulfonyl chloride (172). Bauer and Strauss (20) demonstrated the simultaneous iodination of the imidazole and phenolic groups of globin, but in other proteins the former do not appear to react with iodine (20, 148, 163. 200). Mustard gas and the nitrogen mustards react non-specifically with the imidazole groups of proteins (78, 125, 190).

G. GUANIDYL GROUPS

The guanidyl groups of proteins are those of arginine. Although it would seem likely that this highly charged group, most basic of those in proteins, might be of importance in various biological activities, its rôle has not yet been studied, nor are there available useful specific reagents for such studies.

Experiments in this Laboratory indicate that formaldehyde reacts rapidly with the guanidyl and amide groups of proteins at pH 11–12 at room temperature (107). The derivative of egg albumin, after isolation by dialysis, contained almost the same number of amino and SH groups as the original protein. In tryptophan-free proteins, this technique may prove useful for the preparation of guanidyl- and amide-substituted proteins. A sample of insulin treated by this procedure was found to retain its original activity (117). The guanidyl groups of proteins also react with formaldehyde in neutral and acid solution but the reaction is slow, and amino and amide groups are also involved (112, 316b).

Acylating agents and nitrous acid in acetic acid react with guanidyl groups, but at rates considerably slower than those observed with amino and phenol groups, and under conditions where several other types of groups are also attacked (see Section III). Indications have been obtained (114, 144) that phenyl or chlorophenyl isocyanate may react slowly with the guanidyl groups of protamines, but these reagents like the others mentioned are non-specific. The introduction of nitro groups on the guanidyl residues of proteins by reaction with concentrated nitric acid in the presence of fuming sulfuric acid (191) is obviously of little use for the type of research covered in this review.

H. ALIPHATIC HYDROXYL GROUPS

The free aliphatic hydroxyl groups of proteins are those of serine, threonine, hydroxyproline, and hydroxylysine. The latter two amino acids appear to be of importance only in proteins related to collagen (263).

At low temperatures, concentrated sulfuric acid reacts rapidly with proteins to form acid sulfate esters of the aliphatic hydroxyl groups (266). Since the amino and many other polar groups of proteins do not react, sulfuric acid appears to be more selective in this respect than other reagents so far investigated.

The only other groups that are affected are the SH groups, which give substituted *S*-thiosulfuric acids, and some of the phenol groups which give substituted sulfuric acids after short treatment or sulfonic acids if exposure to the acids is prolonged (108, 130, 266). The phenolic groups react more slowly than do the aliphatic hydroxyl groups. Partial destruction of some other amino acids, particularly arginine, appears to occur if the reaction is allowed to proceed for 24 hr. (216).

This reaction should be of value in studies of the aliphatic hydroxyl groups of biological proteins. Glendenning *et al.* (130; *cf.* 39) showed that insulin that had been sulfated with sulfuric acid retained its activity, indicating that the reaction conditions are not necessarily destructive to the protein molecule.

Repeated treatment with methyl sulfate in cold aqueous alkaline solution has been found to methylate about one-half of the aliphatic hydroxyl groups in silk fibroin (135). Aliphatic hydroxyl groups of proteins are attacked by acylating agents, but generally more slowly than are amino or phenolic groups (see Section III,D,1).

I. CARBOXYL GROUPS

The free carboxyl groups of proteins are those δ- and ε-carboxyl groups of aspartic and glutamic acids not present as amides and those occurring at the ends of the peptide chains.

Felix and coworkers (81, 98, 99, 100) allowed proteins to react with methyl alcohol *saturated* with hydrogen chloride and considered that they had accomplished quantitative esterification of the carboxyl groups. Waldschmidt-Leitz *et al.* (332) and Kiesel and Znamenskaja (189) indicated that these conditions also caused other reactions, such as loss of amide groups, destruction of tryptophan, and hydrolysis of peptide linkages. For example, salmine sulfate after treatment by this technique contained 1.2 per cent amino nitrogen (as per cent of total nitrogen) (332), although the untreated protamine contains no detectable end groups (113).

Carr *et al.* (58) studied the inactivation of insulin with alcohol containing small amounts of acid and suggested that esterification of the carboxyl groups had occurred. The activity was recovered by exposure to dilute alkali. Charles and Scott (63), on the basis of methoxyl and *N*-methyl determinations, expressed doubt that the reaction was a simple esterification. However, their data are at least partly interpretable as showing only the presence of difficultly removable alcohol (*cf.* 130, 182, 225). The inactivation of insulin with acid-alcohol and complete regeneration of activity by mild alkaline hydrolysis has been duplicated recently (195).

When proteins were treated with 0.02–0.1 *N* hydrochloric acid in methanol, their carboxyl groups were found to be almost quantitatively esterified (111). The number of methoxyl groups that could be introduced was in good agreement with the number of carboxyl groups present. Amino, phenolic, indole, and amide groups were shown not to be affected. Esterification occurred with higher primary alcohols, but was progressively (with the molecular weight of the alcohol) slower and less complete. This procedure should prove useful in investigating the rôle of carboxyl groups in those proteins *that will not be denatured under these conditions.*[6] However, the inability of several workers to reactivate esterified proteins, other than insulin, by mild alkaline hydrolysis (117, 202, 326) requires further investigation.

At pH 5.5–6.0, mustard gas [bis(2-chloroethyl) sulfide] appears to esterify a certain proportion of the carboxyl groups of several proteins (167). The amount of mustard introduced is closely equivalent to the carboxyl groups reacted (as determined by titration) (78). Although the tyrosine Folin color is reduced

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[6] Egg albumin was 60 per cent methylated even at −5°C. (2 days) but appeared to be completely denatured. On the other hand, with serum albumin, 45 per cent of the carboxyl groups were methylated under the same conditions, and the product was soluble and heat-coagulable at its isoelectric point (pH 7.3). A negative nitroprusside test (in 8 *M* guanidine hydrochloride) indicated that at some time the SH groups may have been available for autoxidation. In a control experiment, serum albumin, temporarily "denatured" by exposure to 8 *M* guanidine hydrochloride for 30 min. and then recovered by dialysis, was still soluble and heat-coagulable, but the nitroprusside test was considerably decreased.

(167), it appears probable that the phenolic groups are not involved, since no appreciable change in titration between pH 8.5 and 11.0 was observed (78). The difficulty in interpreting Folin color reactions has already been mentioned (see footnote 5). At any rate, there is a possibility that mustard gas may be useful as a specific reagent for carboxyl groups in proteins containing no available SH (or thioether) groups (Section III).

In addition to these reagents, protein carboxyl groups have been esterified by diazomethane, methyl sulfate, methyl iodide, methyl *p*-toluenesulfonate, and 1,2-epoxides, but these reagents generally also attack other groups in the protein molecule (see Section III).

J. AMIDE GROUPS

The amide groups of proteins occur on the ϵ- and δ-carboxyl groups of glutamic and aspartic acids. The proportion of such carboxyl groups that are present as amide differs from one protein to another. Whether part of the ammonia liberated by mild acid hydrolysis might arise also from carboxyl groups at the ends of the peptide chains is not known.

The amide group is comparatively inert. Hydrolysis occurs more rapidly than with peptide bonds (328), but acceptable methods for quantitatively hydrolyzing amide groups *without some hydrolysis of the main chain* have not been described.

The amide groups of proteins react slowly with formaldehyde in neutral or acid solution (110, 345), but under the same conditions amino, guanidyl, and perhaps other groups also react. It has recently been found that protein amide (and guanidyl) groups react rapidly with formaldehyde at room temperature in alkaline solution (107) (see Section II,G). The retention of insulin activity after such treatment (117) suggests that unsubstituted amide (and guanidyl) groups are not essential for the activity of this protein.

K. THIOETHER LINKAGE

The methylthioether linkage of methionine has received no attention in specificity studies. The possibility that hydrogen peroxide may be a useful reagent for the modification of this group is suggested by the observations of Jaques and Bell (184), who correlated roughly the consumption of hydrogen peroxide (0.04 *N*) at pH 6.6 with the methionine contents of fibrin and fibrinogen. Toennies and Callan (320) had previously shown that under certain conditions methionine reacted even more rapidly than cysteine with hydrogen peroxide. The product is the sulfoxide. Methionine in proteins reacts non-specifically with mustard gas at pH 7 and 9, as indicated by nutrition experiments with mustard gas-treated proteins (190). The work of Stein and Moore (310) suggests that *in acid medium* mustard gas may act as a somewhat more specific reagent for the thioether linkage in proteins. The nitrogen mustards also react with methionine (124).

Iodine adds to the thioether linkage of methionine to form a colorless periodide. *N*-Acylated methionine periodides are unstable (197); hence this reaction probably does not occur with proteins.

III. Protein Reagents

A. OXIDIZING AGENTS

The effect of oxidizing agents on the SH groups of proteins has received much attention (10, 19, 31, 139, 157, 158, 159, 297). The following generalizations appear valid. The number of SH groups oxidized depends upon the reagent, the conditions of the reaction, and the relative "availability" of the SH groups. Iodine appears to be able to oxidize some SH groups which are not available to other oxidizing agents (7, 8) and in acid solution the oxidizing action of iodine may be specific (8, 171). In neutral and alkaline solution other reactions occur (see Section III,F). A number of other oxidizing agents have been carefully studied, particularly for the purpose of determining quantitatively the number of sulfhydryl groups in proteins. Ferricyanide (6, 8, 9), porphyrindin (53, 140, 141, 192), iodosobenzoate (159, 160), tetrathionate, and Folin's uric acid reagent (9) have been found to be useful reagents, providing the concentration of reagent, and time, temperature, and pH of the reaction are carefully controlled.

Oxidation of proteins by disulfide compounds such as cystine and oxidized glutathione would appear to be a specific reaction for SH groups. No others in proteins are known to react (174, 237). Since this is an equilibrium reaction, an excess of the reagent is required. Balls and Lineweaver (15) inactivated papain with cystine. It has been suggested (250, 333) that the disulfide obtained from monothioglycol would be a useful reagent of this type.

Other oxidizing agents not yet mentioned that have been used with SH enzymes are hydrogen peroxide, potassium permanganate, and perbenzoic acid (139, 157, 158, 340). Conditions are chosen with proteins such that at least part of the activity can be regenerated by the action of reducing agents. Air oxidation, particularly when catalyzed by heavy metal salts (*cf.* 29), attacks SH groups. The catalytic effect of the cupric ion extends to anaerobic oxidations as well (8, 152). Weill and Caldwell (336) oxidized the SH groups of β-amylase with ferricyanide and cupric ions. Ferricyanide alone was without effect. The catalytic effect of heavy metals is inhibited by small amounts of cyanide (9). The reaction of quinone with the SH group of cysteine is an addition and not a simple oxidation to cystine (128a, 192).

Despite the fact that much useful information has been obtained, the disadvantages of the oxidizing agents outweigh their advantages as specific agents for SH groups. The weaker reagents often do not attack all of the SH groups; the stronger ones attack other groups besides. Even when oxidation of SH groups is complete, as judged by disappearance of the nitroprusside test, and other groups escape detectable reaction, complete reversal of the oxidation (measured by enzyme reactivation) is often not achievable. In these cases, it may be assumed that oxidation of SH groups has proceeded to the sulfonate or to some other intermediate, but non-reversible, stage of oxidation (10, 11).

Other groups are attacked by oxidizing agents when the conditions are more severe than those required for SH groups. Those generally affected seem to be the phenol and indole groups (10, 53, 237). Sizer (298, 299, 300, 302) followed the inactivation of enzymes by oxidizing agents of varying potentials and concluded, from spectrographic evidence, that the phenol groups were oxidized. The effect of oxidizing agents on thioether groups has not been studied in detail, but the known reaction of hydrogen peroxide (see Section II,K) suggests that other oxidizing agents might also react with this group. Lyman *et al.* (217) removed quantitatively the methionine, cystine, tyrosine, and tryptophan from a peptone preparation by oxidation with hydrogen peroxide in acid solution (*cf.* 321). Cysteic acid has been isolated from oxidized keratins (73). The action of hydrogen peroxide (5 per cent) on tobacco mosaic virus resulted in a 60 per cent drop in amino nitrogen (308). The Folin reagent oxidizes phenol and indole (and SH) groups under conditions where most proteins are not denatured. Smetana and Shemin (305) found that exposure of egg albumin to light in the presence of hematoporphyrin caused reversible oxidation of SH groups and progressive destruction of tryptophan and histidine. Tyrosine was apparently unaffected. This is in contrast to the earlier work of Harris (151), who found the amino acids tryptophan and tyrosine, but not histidine, susceptible to such oxidation (*cf.* 59, 208).

Desnuelle and Antonin (79) reacted proteins with periodate. The only groups affected appeared to be side chains of hydroxylysine. If serine or threonine occurred at the amino end of the peptide chain it would also be expected to react under these conditions. Alloxan was suggested as an oxidizing reagent for SH groups by Labes and Freisberger (194), but this compound may also attack the amino (62) and other groups. The toxicities of both alloxan and tetrathionate are ascribed to their SH-combining property (254).

Air oxidation destroys the biological activity of prolan, even though SH groups appear to be absent (37, 48, 142). Several viruses can be stabilized against air inactivation by cysteine (16, 34, 244, 346). The rôle of SH groups in these proteins is not known; however, at least one virus appears to require SH groups for its activity (183). The possibility that easily oxidizable groups other than SH may play important rôles in the biological activities of proteins cannot be dismissed.

B. REDUCING AGENTS

The reagents most commonly employed to reduce the disulfide bonds of proteins have been cysteine, glutathione, thioglycolic acid, monothioglycol, and hydrogen sulfide. They are generally used in excess, and in neutral or alkaline solution (89, 104, 129, 131, 174, 186, 233, 234, 252, 258, 259, 330, 341), but Stern and White (311) used acid media for the partial reduction of insulin. Although Mirsky and Anson (237) and Fraenkel-Conrat (104) found thioglycolate the most effective reducing agent for protein disulfide bonds, Wintersteiner (341) indicated that cysteine, thioglycolate, and thiolactate were equally effective as reducing agents for insulin. This is in accord with the fact that the SH compounds have very similar oxidation-reduction potentials (33, 124, 278). The absence of ionizing groups in thioglycol is an advantage in some studies (250). 1,2-Dithiopropanol (British Anti-Lewisite, BAL) was more effective than other SH compounds for reactivating enzymes that had been inactivated with Lewisite (18a) (see Section III,H).

The action of cyanides on the disulfide linkage is one of addition (222):

$$P{-}S{-}S{-}P + CN^- \rightarrow P{-}SCN + P{-}SH$$

This reaction has found utility in the qualitative test for disulfide bonds by the nitroprusside reagent (7, 8, 10, 333), as a supplementary reagent for SH enzyme activation (139), and in the preparation of reduced keratins (131, 314).

The action of bisulfite ions on the disulfide linkage was shown by Clarke (67; *cf.* 214) to occur as follows:

$$P{-}S{-}S{-}P + HSO_3^- \rightarrow P{-}S{-}SO_3^- + P{-}SH$$

Bisulfite has been used mostly in studies with keratins (41, 93, 94, 186, 230). Maximum reduction of wool occurs at pH 5 (93, 230, 316), but only half of the disulfide bonds are available for the reaction (209, 230). When bisulfited wool is rinsed with water, approximately half of the SH and *S*-cysteinyl sulfonate groups revert to disulfide groups, and the reaction can be reversed completely by treatment with pH 8 buffer for 1 hr. at 50°C.(41).

Phenylhydrazine has been found to activate SH enzymes (13, 340), but the mechanism is disputed (13, 27, 157).

Catalytic hydrogenation has been used to remove iodine from iodinated insulin (148). Removal of approximately two-thirds of the iodine resulted in a corresponding recovery of biological activity. Since the activity of insulin is so dependent upon its intact disulfide groups, these were apparently not reduced under the conditions used. Tests for SH groups were negative. Clutton, Harington, and Yuill (69) and Humphrey and Yuill (179) removed carbobenzoxy groups from *O*-glucosidyl *N*-carbobenzoxytyrosyl insulin by catalytic hydrogenation in alkaline solution, but by the same technique Gaunt and Wormall (128) could not remove carbobenzoxy groups from insulin that had been treated with carbobenzoxy chloride. Freudenberg, Dirscherl, and Eyer (120) inactivated insulin by catalytic hydrogenation. In no case has the formation of SH groups been demonstrated.

Sodium in liquid ammonia was used by Clutton, Harington, and Mead (68) to remove carbobenzoxy groups from the gelatin derivative obtained with *O*-glucosidyl-*N* carbobenzoxytyrosyl azide. This reaction was not applicable to the analogous insulin derivative. Roberts (268) found that insulin was rapidly inactivated by sodium in liquid ammonia. In contrast, the parathyroid hormone was fairly stable to this type of reduction (269). A number of other reducing agents (zinc–acid, tin–acid sodium amalgam, activated magnesium) have been applied to proteins, mostly to insulin (119, 120; *cf.* 116). No specific utility has as yet been demonstrated.

C. ALKYLATING AGENTS

1. Iodoacetate and iodoacetamide

These reagents have been used extensively since Rapkine (261) noted that iodoacetate abolished the nitroprusside test for the SH groups of denatured egg albumin. A thioether is formed (80).

$$P{-}SH + ICH_2COO^- \rightarrow P{-}S{-}CH_2COO^- + I^-$$

Iodoacetamide was used after Smythe (306) reported that it was somewhat more reactive than iodoacetate. The specificity of these reagents for the SH group, originally considered to be complete, has been questioned. Michaelis and Schubert (288) noted that they reacted with the amino groups of amino acids (*cf.* 289), but Goddard and Michaelis (131) and Pillemer *et al.* (258) found no reduction in the amino nitrogen content of kerateins that had been treated with iodoacetate. Rosner (273) obtained no reaction of iodoacetate with native egg albumin, but, after denaturation, there was an immediate rapid reaction, ascribable to the SH groups, followed by a slow continuing reaction. Barron and Singer (19) treated SH enzymes that had previously been reacted with *p*-chloromercuribenzoate, with iodoacetate and iodoacetamide. The activities observed, after reactivation with glutathione, indicated that irreversible damage had been caused by these reagents, presumably at positions in the enzyme other than the SH groups. However, since the reaction with chloromercuribenzoate, unlike that with iodoacetamide, is reversible and therefore continually in equilibrium, the possibility remains that iodoacetamide may have reacted with SH groups even under these conditions. In this Laboratory, marked losses have been observed in the amino nitrogen content of serum albumin and insulin treated with 0.05 *M* iodoacetamide at pH 7.5 or 8.5 for 3 days at 40°C.; *p*-cresol, but not the phenolic groups of these proteins, reacted under the same severe conditions (114). There is thus considerable evidence that iodacetate and iodoacetamide may react with groups other than SH.

In addition, they do not *always* react with SH groups. Maver *et al.* (223) found iodoacetamide relatively ineffective for inactivating a lymphosarcoma cathepsin, the activity of which was dependent upon SH groups, and Anson and Stanley (11) report that 0.05-0.1 *M* iodoacetamide, at pH 8 and 37°C., inactivated tobacco mosaic virus without affecting the SH groups.

The lack of reversibility makes this reaction with SH groups usually less advantageous than that with the mercaptide-forming agents, but does provide an analytical method for determining the SH content of reduced proteins. The total cystine plus cysteine content of the reduced *and* alkylated protein is compared with that of the original (104, 237, 252, 258). The difference represents the amount of cystine in the reduced protein. Reaction with other groups would not defeat this purpose.

In general, it may be concluded that if iodoacetate and iodoacetamide rapidly inactivate a protein at neutrality and room temperature, it is probable that the reaction involves SH groups. In any case, analytical determinations of original and residual SH groups should be made.

2. *Miscellaneous alkylating agents*

A number of other alkylating agents react with SH groups, particularly of reduced proteins. Among these may be mentioned α-halogen acids other than iodoacetate (258), iodoethanol (132), methyl iodide (41, 293), and other alkyl halogen compounds (252). Evidence for specificity is lacking.

The methylation of proteins by methyl iodide, methyl bromide, and dimethyl sulfate has been studied extensively (*cf.* 1, 40, 166). Methyl iodide and bromide were found by Blackburn *et al.* (40, 41) to introduce amounts of methoxyl into several proteins corresponding roughly to their content of free carboxyl groups, but some *N*-methylation also occurred. Charles and Scott (63) found insulin to be inactivated by intensive treatment with methyl iodide. Thirty per cent of the activity was recoverable after dilute alkaline hydrolysis. From the course and extent of reaction and reactivation, and from the fact that iodine was introduced into the protein, they concluded that esterification and subsequent hydrolysis of the carboxyl groups were *not* the primary cause of the observed inactivation. However, it is possible that the technique used (refluxing with methyl iodide in alcohol solution) might have caused esterification of the carboxyl groups by the alcohol. Hydriodic acid, released during the reaction of methyl iodide with other groups, would have acted as catalyst (see Section II,D.

Dimethyl sulfate is similarly non-specific. It has been found to react with phenol, SH, aliphatic hydroxyl, amino, guanidyl, and other nitrogenous groups (1, 40, 42, 98, 99, 135). However, Christensen (66) observed that treatment of tyrocidine with dimethyl sulfate produced extensive methylation of the phenol groups but little, if any, *N*-methylation.

Diazomethane has been used by several investigators. Rutherford, Patterson, and Harris (277) treated silk fibroin with diazomethane and found that the alkali-stable methoxyl groups corresponded in number to those of tyrosine. The alkali-labile ones were presumably esters of the free carboxyl groups. Esterification was also observed by Matula (221). (For previous papers on diazomethane, see references 2, 3, 169.)

D. ACYLATING AGENTS

1. Ketene

This reagent has frequently been used in studies of protein group specificity (table 2). Herriott and Northrop (162, 168) treated pepsin at pH 4–5.5 with ketene gas and found that reaction with amino groups was considerably more rapid than that with phenol groups. Activity was retained during acetylation of the amino groups but decreased proportionately with the acetylation of the phenol groups. Upon prolonged ketenization, more acetyl groups were introduced than could be accounted for by amino and phenol groups only. In a study of insulin, Stern and White (312) observed that ketene attacked amino groups more rapidly than phenol groups. Activity was retained during acetylation of the amino groups but disappeared during prolonged ketenization. These studies were considered by other workers to indicate that rapid inactivation of a biologically active protein with ketene meant that the amino groups were essential and slow inactivation meant that the phenolic groups were essential.

The difficulty in such a generalization is well illustrated by recent work. For example, Li and Kalman (203) have shown that the phenol groups of the lactogenic hormone may be attacked by ketene even more rapidly than the amino groups, and in the case of the parathyroid hormone, Wood and Ross

(342) found both types of groups to become only about 40 per cent acetylated. Selective acetylation of the amino groups has, however, been achieved by Herriott (162) and several subsequent workers, by the expedient of exposing the ketenized preparations to conditions of acidity or alkalinity which have been shown to cause hydrolysis of the labile phenyl acetate but not of the acetylamino or of true peptide or amide linkages.[7]

While the action of ketene on the amino and phenolic groups of proteins has often been studied analytically, determinations of the total number of acetyl groups introduced, which alone could assure non-participation of other types of groups, have been performed in only a few instances. The work of Herriott and Northrop (168), already mentioned, indicated that more acetyl groups were introduced upon prolonged ketenization of pepsin than were accounted for by the amino plus phenolic groups reacted. Sandor and Goldie (279) also found considerable more acetyl groups in ketenized serum proteins than corresponded to the number of amino groups reacted; phenolic groups did not appear to react in this case. Herriott and Northrop (168) suggested that the slow acetylation of aliphatic hydroxyl groups might be responsible for their findings with pepsin. This was in agreement with the known reactivity of ketene (309). Other authors have generally assumed that the aliphatic hydroxyl groups of proteins are not acetylated on the basis of model experiments with glucosamine (27), the carbohydrate constituent of egg albumin (247), and hydroxyglutamic acid (248). However, it has lately been found possible to acetylate by prolonged ketenization some of the hydroxyl groups of sericin and polyvinyl alcohol (114; *cf.* 57, 334). There is thus still a possibility that some of the effects noted with ketene, particularly after prolonged treatment, may be explained on the basis of acetylation of the aliphatic hydroxyl groups. For example, Miller and Stanley (235) found that about 70 per cent of the amino and 20 per cent of the phenol groups of tobacco mosaic virus could be acetylated with ketene without loss of activity. Further acetylation caused a decrease without marked increase in the amount of either amino or phenol groups reacted. Whereas it is possible that this may reflect the acetylation of a small number, perhaps even one sluggish essential amino or phenol group in the virus, the alternate possibility that essential aliphatic hydroxyl or other groups may have reacted deserves consideration. Schramm and Miller, who also studied this reaction intensively (286, 287), could not demonstrate alkaline reactivation of ketene-inactivated tobacco mosaic virus. This should have been possible if the inactivation had been due to acetylation of phenolic groups.

Of the polar groups in proteins not yet mentioned, the SH group is known to react (79a, 105). Those of egg albumin are acetylated by ketene at pH 5–6 more slowly than are the amino groups, possibly only at the rate at which they are unmasked through surface denaturation (79a). The thioacetate groups so formed are rapidly hydrolyzed by dilute alkali.

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[7] The phenyl acetate bond is hydrolyzed by long standing in neutral solution (232, 276). In attempts to determine the extent of acetylation of the phenol groups of proteins by hydrolyzing them with enzymes prior to determination of Folin color, the phenol acetate bonds were found to be split by the condition used for enzymatic digestion (114). The observation that ketene effected only a *temporary* detoxification of gonococcus and meningococcus (46) may be explained if it is assumed that the essential groups gave readily hydrolyzable acetates.

Several model substances were treated with ketene under rather more vigorous conditions than those usually used. Only slightly more acetyl groups were introduced into gliadin and protamine than could be accounted for on the basis of their known amino, phenol, hydroxyl, and SH contents. It may thus be concluded that the amide and guanidyl groups of proteins react with ketene very slowly, if at all (114). The indole groups of gramicidin appeared to be acetylated to a small extent by prolonged ketenization (108). Wood and Ross (342) observed that the chromogenic value of ketenized parathyroid hormone, after dilute alkaline hydrolysis, was 10–15 per cent lower (Folin color) than that of the untreated hormone, from which they inferred that additional chromogenic groups had reacted to form stable acetates. However, interpretations of Folin color changes are difficult (see footnote 5). Neuberger (217) mentioned the possibility that the imidazole groups of proteins might react with ketene in a Bamberger-fission type of reaction, but an intensively ketenized insulin was found to have an unchanged histidine content after hydrolysis (114). This does not exclude the possibility that the imidazole ring may have been acetylated.

It must thus be concluded that ketene falls short of being a good protein reagent in several respects: (*1*) Its action is not sufficiently specific for the amino groups. (*2*) It does not generally attack this type of grouping to completion. (*3*) As an unstable gas it needs special equipment for its preparation, is difficult to employ in accurately known amounts, and tends to surface-denature sensitive proteins. As an additional disadvantage, ketene appears to be extremely toxic (56, 313). It has been suggested that it might racemize some of the asymmetric carbon atoms of proteins if reaction is carried out in acid solution (180).

Acetic anhydride is a preferable reagent where acetylation of protein amino groups is desired.

2. *Acetic anhydride*

Preliminary observations indicate that acetic anhydride may be a valuable reagent for amino groups. The technique used by Hughes (178; *cf.* 166) involves causing a protein in cold sodium acetate-buffered solution to react with a limited amount of the reagent. With several proteins, the number of acetyl groups introduced has been found to be closely equivalent to the number of amino groups originally present (table 3) (114). Some proteins however—lysozyme, crotoxin—did not appear to react to completion. Phenolic groups were affected only slightly if at all. The technique appeared to cause no denaturation, since the acetyl derivative of egg albumin retained its masked SH group, and was heat-coagulable and soluble at its isoelectric point. As mentioned before, it cannot be concluded that acetic anhydride would react with all other proteins in a similar manner. Analytical controls are necessary.

Acetic and higher aliphatic anhydrides and chlorides have been used by many investigators to modify proteins under more violent conditions than those described above. The reaction may then involve SH, phenol, aliphatic hydroxyl, indole, and possibly basic groups in addition to the amino groups (41, 42, 57, 110a, 135a, 136, 161).

3. *Aromatic isocyanates*

Hopkins and Wormall (175, 176) found a fairly close correlation between the amount of bromine introduced into proteins by reaction with *p*-bromophenyl isocyanate and the decrease in amino nitrogen, and concluded that the reagent reacted *only* with the amino groups. In contrast, Miller and Stanley (235) reported that phenyl isocyanate reacted not only with the amino groups but also with 30 to 40 per cent of the phenolic groups of tobacco mosaic virus under the conditions used. Miller (231) later showed that these values were erroneously high. In view of the difficulties involved in interpreting Folin color values (see footnote 5), it now appears that participation of phenol groups in the reaction may not have been definitely proven. It is of interest that inactivation by phenyl isocyanate of tobacco mosaic virus was not demonstrated (235, 287). Fraenkel-Conrat *et al.* (109) found no evidence for the reaction of the phenol groups of egg albumin with phenyl isocyanate at pH 8.0, but recent experiments indicate that even under the mildest conditions insulin combines with more chlorophenyl isocyanate than can be accounted for by its amino groups alone (114).

TABLE 3

Effect of acetic anhydride[a] *on reactive groups of proteins*

PROTEIN	ORIGINAL AMINO-GROUPS[c]	LOSS IN AMINO-GROUPS[c]	ACETYL GROUPS INTRODUCED
	gram-moles/10⁴ g.	*gram-moles/10⁴ g.*	*gram-moles/10⁴ g.*
Bovine serum albumin . . .	8.5	7.9	8.5
Egg albumin . .	4.7	4.0	4.7
Insulin. .	5.0	4.5	4.5

[a] 1.2 parts acetic anhydride was added dropwise to a stirred solution of 1 part of the protein (5 per cent) in half-saturated sodium acetate solution held at 0–15°C.

[b] The SH groups of egg albumin were not affected by the reagent, but it is possible that available SH groups, such as those of myosin, would be acetylated. The phenolic groups, as estimated from the change in Folin color from that of the original protein, were in no case decreased by more than 10 per cent. The colors obtained at pH 8 were 81 to 95 per cent of those obtained at pH 11 (162) (see footnote 5)

[c] Van Slyke manometric procedure (327a); 15 min reaction time.

However, as with acid anhydrides and chlorides, the specificity of phenyl isocyanate may be dependent upon the amount of reagent used. Thus, Sizer (300) found that reaction of one part phenyl isocyanate to two parts chymotrypsin did not destroy the enzyme activity, whereas a reagent–protein ratio of 2.5 to 1 resulted in immediate destruction. Since other experiments indicated that the phenol but not the amino groups of chymotrypsin were essential, this observation suggests that the phenol groups had reacted with the excess phenyl isocyanate. The need for analytical controls is evident.

Phenyl isocyanate reacts with the SH groups of low-molecular-weight compounds (127) and proteins (105). The SH groups of native egg albumin react with *m*-chlorophenyl isocyanate even at 0°C., and more rapidly than do the amino groups (114). Some evidence indicates that the guanidyl groups of proteins may react to a slight extent with phenyl isocyanate in aqueous solution at pH 8 (114, 127, 144).

The isocyanate reaction has been used to introduce several types of aromatic and heterocyclic groups into proteins (76, 272). Where analyses have been made (76), part of the amino groups appeared to have reacted. Jensen and Evans (185) used phenyl isocyanate to show that phenylalanine occurred at the amino end of some of the peptide chains in insulin. Roche *et al.* (270) have recently extended this technique to several other proteins.

The usefulness of aromatic isocyanates as specific agents for the amino groups of proteins is limited by the possibility of reaction with the phenol groups and also by the following additional disadvantages. The reagents and their reaction products with water are water-insoluble, and the protein derivatives also may be quite insoluble in aqueous solution (109). This insolubility makes difficult both the interpretation of biological assays and also group analyses by colorimetric analytical methods. Attempts to determine the degree of involvement of phenol groups have been unsatisfactory; the derivatives resist enzyme digestion (114), and mild alkaline treatment yields aniline which contributes to high Folin color values (232).

4. Carbon suboxide

The reaction of carbon suboxide with proteins has been studied in some detail (322). This compound is a gas resembling ketene in many of its properties. It reacts at similar rates with the amino and phenolic groups of serum albumin and, presumably, other proteins. Both types of groups can be almost completely substituted. The derivatives are half-amides and half-esters of malonic acid. The phenolic ester is readily hydrolyzed, even at neutrality. Tracy and Ross (323) found that carbon suboxide inactivated pepsin, and that part of the activity was regained after gentle hydrolysis, in agreement with Herriott's findings (162, 163) concerning the essential rôle of the phenolic groups for peptic activity.

Carbon suboxide (at pH 5–6) attacked the SH groups of native egg albumin more rapidly than it did either the amino or the phenolic groups (105). Model experiments with amino acids suggest that imidazole, guanidyl, and aliphatic hydroxyl groups do not react (274). The lability of the phenolic ester makes possible the use of carbon suboxide as a specific reagent for amino groups, since derivatives can be freed of all but amino-bound malonyl groups by mild alkaline hydrolysis. The derivatives are of interest in that the substitution of a free carboxyl group for each amino group results in proteins with isoelectric points considerably lower than those of the original proteins. However, most of the disadvantages listed for ketene are equally valid for carbon suboxide.

5. Miscellaneous

The Schotten-Baumann technique has been used with benzoyl chloride and benzoic anhydride to introduce benzoyl groups into proteins. Selectivity can be achieved by the use of minimum quantities of the reagent. Thus Mellon *et al.* (226) treated casein with benzoyl chloride and found that, until more than 50 per cent of the amino groups had been acylated, only negligible amounts of extra benzoyl were introduced. With more vigorous reaction conditions, benzoyl groups can be introduced also on many other polar groups. Goldschmidt and Schön (134) used benzoic anhydride. Goldschmidt and Kinsky (133) carefully acylated egg albumin with *m*-chlorobenzoyl chloride. They showed that part of the acyl groups introduced were attached to the amino groups and that these were quite resistant to hydrolysis, while the rest were of varying lability to alkali at low temperatures. Other studies are in agreement (2, 3). Benzoyl chloride also reacts with the imidazole and guanidyl groups of protamines (81, 98). The possibility that the imidazole groups of proteins may undergo a Bamberger fission with benzoyl chloride has been suggested (309).

Carbobenzoxy chloride has been used with insulin (128) and tobacco mosaic virus (236). It appeared to attack amino groups more specifically than ketene, phenyl isocyanate, *p*-chlorobenzoyl chloride, or benzenesulfonyl chloride since, for the same number of amino groups reacted, there were fewer phenolic groups involved. Benzenesulfonyl chloride was used by Gurin and Clarke (143) with gelatin. About 30 per cent more sulfur was introduced than could be accounted for by the decrease in amino groups. In pyridine solution, toluenesulfonyl chloride attacked the phenol groups of tyrocidine more rapidly than it did the amino groups (66), contrary to the usual order of reaction of acylating agents in aqueous solution.

Azides react with proteins in cold aqueous alkaline dioxane (54, 68, 69, 70, 179, 229). Clutton *et al.* (68) suggested that reaction occurred only with the α-amino nitrogen groups, but more of the reagent (*O*-glucosido-*N*-carbobenzoxytyrosyl azide) was introduced than could be accounted for on this basis (69), and the titration curves also did not conform to this hypothesis (68). The serum globulin derivative was heat-coagulable (69).

Phosphorylation of proteins has been accomplished by reaction with phosphorus oxychloride in dilute alkaline solution (156, 224, 267). Phenol, amino, aliphatic hydroxyl, and other groups probably are involved (224). In contrast, treatment with phosphorus pentoxide dissolved in phosphoric acid appears to achieve phosphorylation of the hydroxyl groups without involving many of the other polar groups (101). The biological activity of insulin is largely retained after such treatment (117).

E. NITROUS ACID

The reaction of nitrous acid with the amino groups of proteins is the basis for the Van Slyke methods for their determination (327). In addition, phenol, SH, and other groups are involved. According to Philpot and Small (256), in the presence of excess nitrite, the reaction with the amino group is "pseudobimolecular," and that with the phenol groups is "unimolecular." Investigators have used rate studies to interpret the results of the reaction of nitrous acid on biological proteins. Usually, if inactivation is rapid, it is concluded that the amino groups are essential; if slow, the phenol groups are considered to be necessary, particularly if the rate of inactivation conforms to a first-order reaction (137, 211, 300, 335).

Philpot and Small (256) studied the action of nitrous acid on pepsin. Under the conditions used (pH 4.0, 1 *M* sodium nitrite, 0°C.), the reaction with the amino group appeared to be essentially complete in 30 min., while reaction with the phenolic group had scarcely begun. Weill and Caldwell (335) identified the first reaction of nitrous acid on β-amylase as an oxidation, presumably of SH groups, since the inactivation could be completely reversed by reducing agents. The slower, irreversible inactivation was considered to be due to reaction with the phenolic groups. It has recently been found that, with the mild conditions used by Philpot and Small (256), most of the SH groups of egg albumin were oxidized, but the amino and phenolic groups were only slightly affected; serum albumin showed a partial loss (about 40 per cent) of the latter two types of groups (114). Philpot and Small (256) showed that the rate of reaction of the phenol groups of pepsin was the same as that of tyrosine (as measured by color development). When the reaction slowed, about 50 per cent of the phenol groups had reacted and 50 per cent of the peptic activity had been destroyed. Since tryptophan reacted much more rapidly than tyrosine with nitrous acid, these authors concluded that the indole groups in pepsin could not be involved in the inactivation by nitrous acid. However, the rate of reaction of the indole groups in pepsin may well differ from that of the amino acid. The difficulty in relying on rates of reaction for information concerning reactive groups is illustrated in a recent paper in which Li (200) showed that the rate of iodination of the phenol groups of serum albumin was accelerated in the presence of urea, to a rate even more rapid than that of tyrosine itself. A study of the effect of denaturants on the extent and rate of reaction of nitrous acid on pepsin might yield interesting information.

The reaction of nitrous acid with tyrosine or the phenol groups of proteins has been shown to involve (*a*) introduction of a nitroso group ortho to the hydroxyl, (*b*) reduction of the nitroso group to an amine, and (*c*) diazotization of the amino group (241, 256). The observations of Eagle (85) indicate that similar reactions may occur with tryptophan and the indole groups of proteins. Extensively "deaminated" proteins have decreased histidine (313, 338), arginine (313), and cystine (170) contents. However, the effect of short-time nitrous acid treatment on the indole, guanidyl, and imidazole groups and on the disulfide linkages of proteins has not been investigated. Studies with the amino acids have shown that tryptophan, arginine, and cystine are attacked slowly (282).

The many reactions that may occur when nitrous acid reacts with proteins would appear to limit its usefulness as a specific reagent. Certainly it should not be used to show the essentiality of SH, amino, or phenol groups without thorough analytical control and separate confirming experiments with different reagents.

F. IODINE

Iodine has been used both as an oxidizing and as a substituting reagent. In dilute acid solutions, particularly of high iodide concentration, oxidation of SH groups appears to be fairly specific. The SH groups of native egg albumin could be completely oxidized at pH 3–5 by stoichiometric amounts of iodine if the oxidation was carried out at 0°C. and in 1 *N* potassium iodide (10, 11). The SH group was oxidized beyond the disulfide stage unless the reaction mixture was kept cold (8). On the other hand, the SH groups of tobacco mosaic virus reacted with iodine at neutrality only in solutions of *low* iodide concentration and in the presence of excess iodine (2.5 times the stoichiometric amount) (11). The virus remained active under these conditions, but with increasing amounts of iodine and at elevated temperature, substitution of the phenol groups and inactivation occurred. Iodine has often been used as an oxidizing agent in the study of SH enzymes (*cf.* 31, 157, 158, 223, 336).

In neutral and alkaline solution, iodine has found utility as a reagent for the phenol groups. Li (198) and Berger and Shaffer (26) studied the kinetics of the reaction of iodine with tyrosine and concluded that they were explainable on the assumption that hypoiodous acid is the primary iodinating reagent. The rate of reaction was inversely proportional to the hydrogen-ion concentration and the square of the iodide concentration and directly proportional to the buffer concentration (199a). These conclusions are in accord with the observations that an acid medium and high concentrations of iodide are preferable when oxidation of SH groups is the desired objective.

Harington and Neuberger (148) iodinated insulin in aqueous or alcoholic ammonia solution. The product had an iodine content of 15.4 per cent, corresponding to the formation of diiodotyrosine quantitatively from the tyrosine residues. The Millon test was negative, and the activity was reduced to 10–15 per cent of that of insulin itself. Seventy per cent of the iodine could be removed by catalytic hydrogenation, and 30–50 per cent of the original activity was thereby regained.

Neuberger (246) obtained an iodinated zein of iodine content conforming to its tyrosine content, and Li *et al.* (204) obtained similarly good agreement with the iodine content of iodinated lactogenic hormone and its original tyrosine content. Herriott (163) studied the iodination of pepsin and identified at least 82 per cent of the iodine as diiodotyrosine in an hydrolysate. In a further study, Herriott (165) added limited amounts of iodine to pepsin, then accounted for 65 per cent of the introduced iodine as monoiodotyrosine. Only 2 per cent of the total phenol groups were involved. The identity of this compound has been questioned (149) and defended (166). Ludwig and von Mutzenbecher (213) accounted for 39 per cent of the iodine in an iodinated casein preparation (total iodine content, 3.5 per cent) as *dl*-monoiodotyrosine. However, kinetic studies on the iodination of tyrosine (198) indicated that the introduction of the first iodine atom is the rate-controlling step, the reaction of the second atom being so rapid that there is very little monoiodotyrosine in the reaction mixture at any particular time. Experiments with lactogenic hormone appeared to be in accord with the concept that iodination of protein phenol groups follows a similar course (204). The mechanism of iodination of the tyrosine groups in proteins may require reinvestigation.

Li (200) found that the rate of fixation of iodine by serum albumin and pepsin was a function of the degree of denaturation. Whereas with the native proteins the rate was slower than with tyrosine, the addition of iodine in urea solution was more rapid, and in heated urea solution the reaction rate exceeded that observed with the free amino acid.[8] These data are interpreted as revealing an increased availability of the tyrosine groups with increasing denaturation. Analytical results indicated that the amount of iodine introduced was equivalent to the amount of tyrosine reacted as determined by the Lugg procedure (215); hence other groups could not have been affected. It may be mentioned that monoiodotyrosine, if present, would give a color by this method (149, 165, 269a).

The papers so far cited appear to show that iodine in nearly neutral or alcoholic or aqueous ammoniacal solution reacts solely with the tyrosine groups of proteins (containing no SH groups). However, Pauly (253) found sturine to bind an amount of iodine which corresponded to its histidine content, and Bauer and Strauss (20, 21, 22, 23) found that globin bound iodine in excess of that required for its tyrosine content and showed that iodination of the imidazole groups had occurred. In this connection it is interesting to note that globin iodinated with limited amounts of iodine did not show the expected change of dissociation constant in alkaline solutions (72), characteristic of proteins containing iodized tyrosine (246). Li (199) found that the rate of iodination of tyrosine was 30 to 100 times faster than that of histidine and pointed out that the imidazole groups of proteins may react with iodine if the reagent is present in excess and the reaction time is prolonged. But Brunings (53a) has shown that the iodination of histidine requires more vigorous conditions than that of histidine anhydride; hence imidazole groups in proteins may react at rates considerably different from those observed with histidine itself.

The possibility of the reaction of the indole groups of proteins with iodine has not been properly assessed. Chymotrypsinogen (6 per cent tryptophan) did not add iodine in dilute acid solution (7), but, at pH 7, acetyltryptophan and gramicidin (40 per cent tryptophan content) decolorize iodine rapidly (114), suggestive evidence that indole groups in proteins may react similarly. It is necessary to postulate that imidazole and indole, and even other groups, can add iodine in order to account for the very large amounts introduced into some proteins by recent workers (45, 155, 245, 294; *cf.* 42a).

Evidence is presented by Philpot and Small (257) that pepsin may be inactivated by small amounts of iodine without participation of the phenol groups in the reaction, but interpretation of the work is rendered difficult by their reliance on the Folin color reaction (see footnote 5) to detect changes in the phenol groups.

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[8] From the results of unpublished experiments, Anson (9, 10) suggests that the oxidation of tyrosine itself may be accelerated in the presence of urea.

Thus, with iodine, as with the other reagents previously discussed, additional analytical work appears to be required before its usefulness as a specific reagent for the phenol groups can be assured.

Under more extreme conditions, iodine converts the tyrosine of proteins into thyroxine (146, 213, 264). Discussion of this interesting reaction is outside the scope of this review.

The effects of bromine and chlorine on proteins under mild conditions have been studied in much less detail. Wormall (344) reacted serum proteins with bromine water and found the product to contain 4.7 per cent bromine. Blumenthal and Clarke (44) showed that bromine water oxidized some protein disulfide bonds to sulfate. Although considerable amounts of chlorine reacted with serum proteins, none was introduced (344); the reaction appeared to be exclusively oxidative. Consden *et al.* (73) demonstrated the presence of cysteic acid in chlorinated wool. Stumpf and Green (316a) found dilute chlorine solutions to inactivate SH enzymes but not to affect enzymes not requiring this group. The strong oxidative properties of these halogens make them of doubtful utility as specific reagents.

G. FORMALDEHYDE

The reaction of formaldehyde with proteins is complicated and its usefulness as a specific reagent is, therefore, limited. An excellent review of the published work until 1945 is available (118). Additional important papers have since appeared, but unless evidence of reaction with specific groups was presented, they have not been quoted in this brief summary.

In neutral solution, the immediate reaction with proteins is combination with the free amino groups (basis for the "formol titration"). However, this is an equilibrium type reaction and is partly or completely reversible by dilution, dialysis, in the presence of the formaldehyde precipitant, dimedon, or under the conditions of the Van Slyke amino nitrogen analysis. With longer time of reaction, the formaldehyde slowly becomes more firmly bound and the amino nitrogen content is decreased (212, 331). Even the latter reaction is partially reversible by dialysis against dilute acid (114, 275). Thus it may be expected that the results obtained with formaldehyde treated, biologically active proteins would depend to a large extent not only upon the reaction conditions used, but also upon the techniques applied to the protein from the time the reaction was completed until the derived protein was assayed.[9]

Instances of reactivation of formaldehyde-inactivated proteins have been observed for bacteriophage (290), Type I pneumococcus antibody (65), parathyroid hormone (326), and tobacco mosaic virus[9] (275). In some cases where the immediate reaction with formaldehyde has been used to demonstrate the essentiality of amino groups, the assay has been performed on the solution containing formaldehyde (207, 210). It is reasonable to suppose that activity might have been regained if the formaldehyde had been removed as, for example, by dialysis. However, when the reaction is permitted to proceed for longer periods of time, the changes that occur are progressively less reversible by dialysis (114).

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[9] Different techniques in the handling of their preparations may explain the inability of Kassanis and Kleczkowski (188) to repeat the reversible inactivation of tobacco mosaic virus by formaldehyde demonstrated by Ross and Stanley (275).

The guanidyl group also reacts slowly with formaldehyde at neutrality and room temperature (107, 112, 316b). Eaton (88) found the Sakaguchi test for guanidyl groups to be decreased in diphtheria toxin treated with formaldehyde, but Ross and Stanley (275) found no change in this test with formalized tobacco mosaic virus.[10]

In alkaline solution, not only the amino, but also the indole (108), amide (107), and guanidyl groups add formaldehyde rapidly (107, 316b). The amino compound, like that obtained at neutrality, is reversibly dissociable. The other combinations are more stable, thus making it possible to obtain protein derivatives in which the amide, indole, and guanidyl, but not the amino groups, are combined.

The reaction of protein SH groups with formaldehyde has not been studied in detail. Anson (8) indicated that those of egg albumin react only slowly with formaldehyde. The SH groups of native egg albumin seem to be largely unaffected by formaldehyde at room temperature and neutrality, although a readily dissociable compound may be formed (114; *cf.* 262, 288).

A number of investigators have reported variable or slow inactivation of biological proteins with formaldehyde. Where analytical data were not obtained, the results have not been included in table 2. The following references include a partial list (24, 35, 38, 43, 60, 275, 326).

Exact interpretations of the reaction of formaldehyde with proteins are complicated by cross-linking reactions. Cross-linking of guanidyl groups has been demonstrated with protamine (112). Of more general significance may be the condensation reaction of aminomethylol groups ($RNHCH_2OH$) with amide, imidazole, indole, phenol, and perhaps still other groups to give stable methylene linkages. These reactions can occur under conditions where neither the amino nor the other polar groups by themselves give stable formaldehyde addition products, or where they do so only slowly (114). Many toxoid preparations require long periods of incubation, e.g., 2 weeks at 37°C., conditions which are favorable for cross-linking. It is thus possible that groups that do not by themselves combine with formaldehyde, may be involved in toxoid formation through the secondary cross-linking reactions.

H. MERCAPTIDE-FORMING AGENTS

The advantages of organic mercury and trivalent arsenic compounds as specific agents for SH groups have been discussed in Section II,A. Of these, *p*-chloromercuribenzoate, first proposed by Hellermann (158), has been the most useful. Phenylmercuric nitrate depresses the activity of non-SH enzymes (74, 75). Various trivalent arsenicals (19, 297) as well as other mercury compounds (19, 158, 159, 336) act similarly, although their effectiveness appears to vary (19, 223). Results with arsenious oxide derivatives should be interpreted with caution, since they may reduce disulfide linkages. Bersin (30) reported that *p*-aminophenylarsenoxide may partially activate papain (*cf.* 71).

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[10] Ross and Stanley (275) observed a decrease in the Folin color value, but this has been recognized as an illustration of the pitfalls of the colorimetric technique (108, 188; footnote 5).

Stocken and Thompson (314) treated a reduced keratin (hair) preparation with lewisite (chlorovinyldichloroarsine). The amount of arsenic bound and its stability suggested that one arsenic molecule combines with two SH groups.

I. MISCELLANEOUS

1. 1,2-Epoxides

Low-molecular-weight, water-soluble epoxides such as ethylene oxide and 1,2-propylene oxide react readily with proteins under mild conditions (106). The carboxyl, amino, phenolic, and SH groups react to form esters, substituted amines, aromatic ethers, and thioethers, respectively. Reaction with amino groups occurs much more readily in alkaline than in acid solution. The products, like other esterified proteins, show isoelectric points raised by 2 to 3 pH units. Attempts to make this a specific technique of esterification have not been successful, since the phenolic groups appeared to react under all conditions used. This conclusion was drawn from Folin analyses and may need substantiation (114).

2. War gases: mustard gas and nitrogen mustards

Some of the extensive work accomplished during the war on the reaction of various war gases on proteins has now been published in detail. The data so far available indicate that many protein groups may participate, but it appears probable that reaction with SH groups may be the most rapid and also that responsible for the intense physiological reactions (17, 102, 138, 153, 235a; *cf.* 166). According to Kinsey and Grant (190) mustard gas [bis(2-chloroethyl) sulfide or H] reacts with protein imidazole, amino, thioether, and hydroxyl groups of threonine at pH 9.3. At pH 7.4, the hydroxyl group does not react. Microbiological assays of H-treated casein hydrolysates indicated that both thioether and amino groups reacted more completely at the higher pH. Herriott *et al.* (167) and Banks *et al.* (17) found the amino content of proteins unchanged after H-treatment at pH 5-6 (*cf.* 240). Carboxyl groups reacted over a wide range of pH values, and this reaction appeared to be fairly specific at pH 5.5-6.0 (with the possible exception of SH groups), since the amount of H introduced into several proteins was roughly equivalent to the number of carboxyl groups esterified (78, 167). However, the extent of involvement of phenol groups is not known (see Section II,I), and the rôle of methionine was not studied.

Model experiments indicate that H may react *in acid solution* primarily with the thioether linkages of proteins to form sulfonium-type addition compounds (310). It has been reported that the imidazole groups react with H at pH 7.6 (78, 190, 243, 329).

Other war gases and related compounds have been studied in somewhat less detail. Fruton *et al.* (125) concluded from model experiments with amino acids and amino acid derivatives that the nitrogen mustards (e.g., bis(2-chloroethyl)-methylamine, etc.) would react with the (*1*) imidazole groups, (*2*) thioether groups, (*3*) amino groups (less rapidly with the ε than with the α), and (*4*) the free carboxyl groups of proteins.

Mustard sulfone, mustard sulfoxide, divinyl sulfone, and other derivatives also react with proteins but fewer details are yet available (17, 25, 307). Mustard sulfone (HO_2) reacts primarily with the SH and amino groups of proteins (17). Reaction with the latter differentiates this reagent from H (25). The sulfoxide (HO) does not react with proteins (17). Divinyl sulfone reacts with protein SH groups (138) and possibly also with the amino and phenol groups (307). Mustard and other war gases have been found to cause mutations in *Drosophila*. The results of investigations so far described indicate that chemical reactions are responsible (11a).

3. Aldehyde and ketone reagents

The activities of a few enzymes are markedly inhibited by low concentrations of hydrazine, hydroxylamine, and semicarbazide (e.g., 123, 126, 220, 318). The conclusion is drawn that the enzymes possess a keto or aldehyde group essential for their activity. However, such results should be ascribed to the presence of prosthetic groups or coenzymes containing ketone or aldehyde groups (such as pyridoxal). No protein group is known to react with these reagents in the low concentrations used. The inhibiting effect of phenylhydrazine on a papain preparation (27) has not been adequately explained.

IV. DISCUSSION

Table 4 contains a compilation of the effects of protein reagents on the various groups, assigned somewhat arbitrarily on the basis of information in the literature and experience gained in this Laboratory. The practice of using several reagents for determining the essentiality of any one group for biological activity is sound, and thorough analytical control of each reaction is strongly recommended.

Table 2 contains much of the data in the literature on the essential groups of biologically active proteins. Knowledge in this field is still fragmentary, but may be expected to expand rapidly with the development of new specific reagents and the accumulation of more information concerning those that have already been found useful. Reagents tagged with radioactive or other isotopic elements should prove extremely helpful in determining the amounts introduced into proteins.

The concept has been tacitly accepted that biologically active proteins have essential groups and that, when these are "covered" or "substituted", the protein can no longer function. This oversimplification is necessary because of the limited information yet available. However, it might be pertinent to mention some of the factors that may complicate the interpretation of the effects of modifying reagents. For example, esterification of the carboxyl groups of insulin results in inactivation (table 2). Is this due to the essentiality of carboxyl

TABLE 4

*Effects of reagents on protein groups under conditions most favorable for specificity**

REAGENTS	AMINO	GUANIDYL	IMIDAZOLE	INDOLE	ALIPHATIC HYDROXYL	AMIDE	THIOETHER	DISULFIDE	SULFHYDRYL	PHENOL	CARBOXYL
Oxidizing agents:											
Iodosobenzoate, porphyrindin, ferricyanide, iodine[a]	–	–	–	–	–	–	–	–	3+	–	–
Hydrogen peroxide[b]					–	–	2+		3+		–
Reducing agents:											
Cysteine, thioglycolic acid, thioglycol, cyanide, sulfite[c].	–	–	–	–	–	–	–	3+	–	–	–
Alkylating agents:											
Iodoacetate, iodoacetamide[d].	±					–		–	2+	±	–
Dinitrofluorobenzene[e]	3+	–	+			–		–	3+	3+	–
Acylating agents:											
Ketene[f]	3+	–		±	±	–	–	–	+	2+	–
Acetic anhydride[g]	3+	–	–	–	–	–	–	–	–	±	–
Phenyl isocyanate[h]	3+	±			–	–	–	–	3+	?	–
Carbon suboxide[f]	2+	–	–		–	–	–	–	3+	2+	–
Azides, benzoyl, carbobenzoxy, benzenesulfonyl chlorides, etc.[i]	3+				–	–	–	–	+	±	–
Concentrated sulfuric acid[j]	–	–	–	–	3+	–	–	–	3+	+	–
Nitrous acid[k]	3+	–		+?	–	–		–	3+	2+	–
Iodine[l]	–	–	±	+?	–	–			3+	3+	–
Formaldehyde (pH 7-8)[m]	(3+)[m]	+		–	–	–	–	–	±	–	–
Formaldehyde (pH 11)[m]	(3+)[m]	3+	–	3+	–	3+			+	–	–
Epoxides[n]	+				–	–		–	2+	2+	3+
Mustard gas[o].	–	–	+		–	–	+	–	3+	?	2+
Acid-alcohol[p].	–	–	–	–	–	–	–	–	–	–	3+
p-Chloromercuribenzoate[q]	–	–	–	–	–	–	–	–	3+	–	–
Diazonium compounds[r].		–	3+	+	–	–	–	–		2+	–

* The symbols used have the following significance: 3+, 2+, and + indicate the relative rapidity or extent of reaction, with 3+ denoting the most rapid reaction. ± indicates reactions that may or may not occur under the conditions suggested. – indicates those reactions either that have been shown not to occur or that appear improbable from organic chemical considerations. ? indicates those reactions for which more information is required. Spaces have been left blank where there is a possibility of reaction but no evidence is available. Allocation of the proper symbols for each reaction is difficult because of the differences between proteins. The choices are arbitrary.

The conditions of the reaction given in the following footnotes are those suggested by users of these reagents. For references to the original literature, see table 2 and the text.

[a] pH 7, 0.001–0.01 *M*, 0–25°C., 5–30 min. The specificity of *iodine* as an oxidizing agent requires a high concentration of iodide ions, pH 1–7.

[b] pH 6.6, 0.005 *M*, 25°C., 0.5–40 hr.

[c] pH 7–8, 0.001–0.1 *M*, 25°C., 0.5–4 hr.

[d] pH 7–8, 0.05–0.1 *M*, 0–25°C., 0.5–2 hr.

[e] pH 7–8, 0.17 *M*, 25°C., 2 hr.

[f] pH 5–8, 0–25°C., 5–30 min.

[g] pH 7–8, 0°C., 30 min. (see table 3).

[h] pH 7–8, 0–25°C., 0.5–2 hr., reagent–protein ratio, 0.5–2.5:1.

TABLE 4—*Continued*

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[i] pH 7-9, 0-25°C., 0.5-2 hr., limited amounts of reagent.

[j] −18° to 0°C., 10-30 min.

[k] pH 4, 1 *M*, 0°C., 30 min.

[l] pH 5-11, −5° to 25°C., 0.5-3 hr., limited amount of iodine, low iodide concentration. See also footnote a.

[m] 25°C., 1-2 *M*, at pH 7-8, 1 hr.; at pH 11, 10 min. Amino groups react rapidly but reversibly. After isolation by dialysis, amino groups are essentially free.

[n] pH 5-6, 1-2 *M*, 25°C., 1-4 days.

[o] pH 5-6, 25°C., 0.5-4 hr.

[p] 0.01-0.1 *M* mineral acid in absolute alcohol, 0-25°C., 1-2 days.

[q] pH 7, 10^{-5} to 10^{-2} *M*, 25°C., 5-30 min.

[r] pH 7-9, limited amounts of reagent, 25°C., 30 min.

groups, or to a change in the charge distribution in the protein? The latter interpretation is favored by the observations of Reiner and Lang (265), who noted that insulin derivatives with azo compounds containing basic groups were inactive while those containing acidic groups were active, although, presumably, the same protein groups were involved. Similarly, the introduction of strongly charged acid sulfate groups on the hydroxyl groups did not destroy insulin activity (130); possibly the introduction of basic substituents *at the same place* would be detrimental. In all cases, including those just mentioned, the possibility must be considered that the formation of a derivative of a "non-essential" group might influence unfavorably the activity of an adjacent but unreacted "essential" group.

Possibly of greater importance than the determination of the essentiality of various groups of biologically active proteins, will be studies of the properties of those derivatives that retain activity. For example, the transformation of toxins to toxoids has so far been accomplished only by empirical methods. In these cases one biological activity (toxicity) is changed, while another (antigenicity) is retained. Knowledge of the groups involved should lead to better control of these processes (*cf.* 251). Similar selective changes in the activities of enzymes and hormones may be possible, but this field has hardly been touched (*cf.* 323). Tobacco mosaic virus can withstand considerable chemical modification without loss of activity (11, 235, 236, 286). Some partially inactivated derivatives were found to have differing specific activities when assayed on different plants (236). Although the derivatives so far obtained all have propagated as the original virus, possible means of producing "chemical mutants" have not yet been exhausted.

It is to be hoped that the application of specific reagents to these various types of proteins will help to enlighten the mystery concerning their mode of function in the life process.

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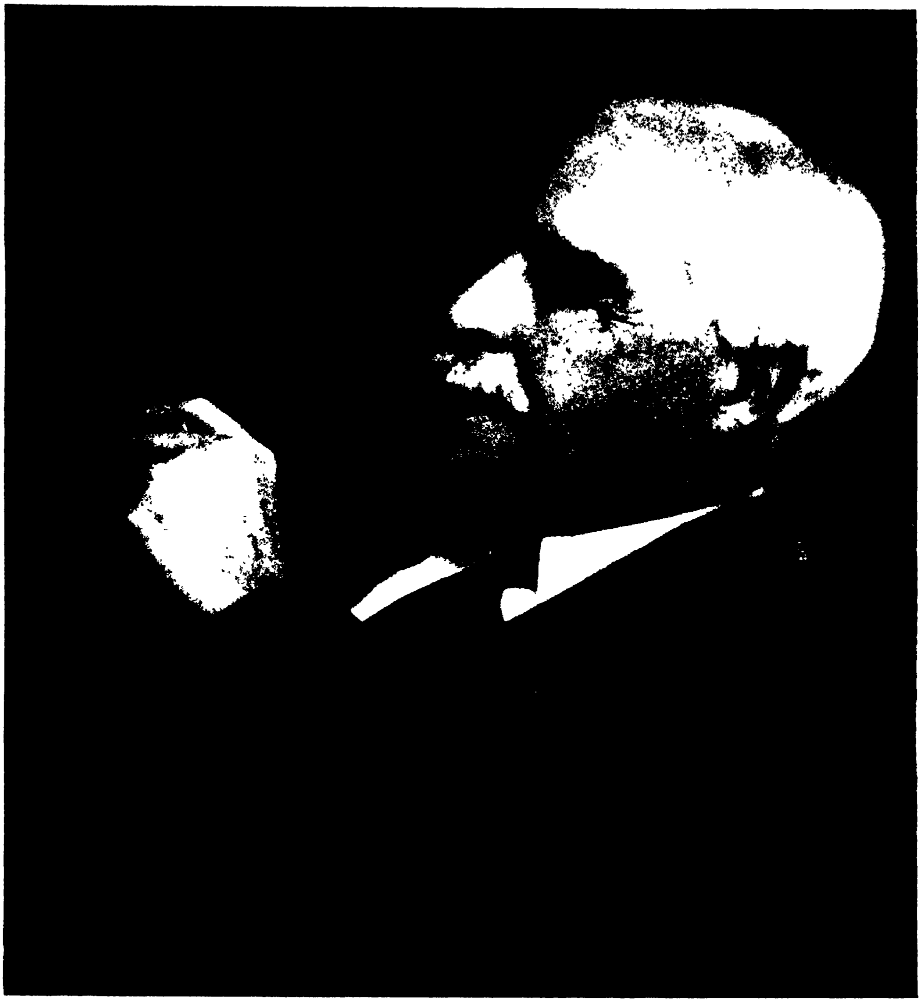

Gilbert Newton Lewi

SYMPOSIUM ON COLOR AND THE ELECTRONIC STRUCTURE OF COMPLEX MOLECULES

DEDICATION

When the Executive Committee of the Division of Physical and Inorganic Chemistry began its consideration of plans for a symposium dedicated to the memory of Gilbert Newton Lewis, it wished to choose a field in which he had won fame. The choice was difficult, because it was not to one field alone that Professor Lewis had directed his scientific interest but to many, and in each of them he had made discoveries and opened roads for further exploration. Physical chemists engaged in the study of thermodynamics regard him as one of the great in that field; the chemists working in the field of structural chemistry call him the father of the modern concept of the chemical bond; and those interested in isotopic research claim him as one of their pioneers because of his work with heavy water. These are a few on the long list of subjects enriched and clarified by his genius.

The Committee thought it fitting to select as the subject of the symposium the optical studies of complex molecules, including fluorescence and phosphorescence of dyes. That is the field in which Professor Lewis was engaged during his last years and even in the very last days of his life. A symposium in that field was the more suitable, since a similar one had been planned at a time when there was abundant hope that Professor Lewis himself would be able to participate in, lead, and inspire the discussion. Unfortunately, that plan could not be realized, but the resulting symposium showed again that whatever Lewis touched will bear the imprint of his great personality through the years to come.

SYMPOSIUM ON COLOR AND THE ELECTRONIC STRUCTURE OF COMPLEX MOLECULES

ORGANIZATION OF THE SYMPOSIUM

This issue of *Chemical Reviews* contains most of the papers contributed to a symposium sponsored by the Division of Physical and Inorganic Chemistry of the American Chemical Society. The sessions of December 30, 1946 were held in the Technological Institute of Northwestern University in Evanston, Illinois. The other sessions were held in Thorne Hall Auditorium of Northwestern University, in Chicago, on December 31, 1946.

The program was arranged by Paul C. Cross of Brown University, who also presided at the opening session. Presiding officers at the later meetings were: P. M. Gross of Duke University (Chairman of the Division, 1946–47), James Franck of the University of Chicago, and F. T. Gucker of Northwestern University. T. F. Young, a former student of G. N. Lewis and Divisional Chairman for 1945–46, and James Franck prepared the dedicatory statement.

To all of these participants and to the contributors of papers, the 1945–46 Executive Committee of the Division of Physical and Inorganic Chemistry expresses its appreciation for their coöperation.

QUANTUM-MECHANICAL METHODS AND THE ELECTRONIC SPECTRA AND STRUCTURE OF MOLECULES[1]

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This paper presents a review of the past and present state of development of the application of quantum mechanics to problems of molecular structure and spectra. Following this, various methods and problems are discussed with emphasis on the desirability of extensive development of semiempirical methods, using either the AO (atomic orbital) or the MO (molecular orbital) method of approximation. It is remarked that the MO method has special advantages when spectra as well as the structures of normal molecules are to be considered. In conclusion, two important needs are pointed out. One is the production of an authoritative compilation of quantitative data on the spectra of pure compounds. The other is a more general familiarity with and a more extensive application of existing possibilities for using quantum mechanics to understand molecular electronic energy levels and spectra.

I. THE PAST AND PRESENT

Dirac once stated that, in principle, the whole of chemistry is implicit in the laws of quantum mechanics. That theory, born in 1925–26, immediately showed itself fruitful for the understanding of the structures of atoms, molecules, and extranuclear matter in general. In particular, it gave the first real qualitative and roughly quantitative explanation of covalent chemical binding. A large proportion of the world's theoretical physicists rushed into quantum-mechanical explorations and computations in the hope that a quantitative understanding of atoms and molecules could now be realized. There was much successful slashing of virgin timber during the period 1927–34. The most striking success of theory was attained, perhaps, in the computations of Hylleraas on the helium atom and of James and Coolidge on the hydrogen molecule. Here quantum mechanics was shown capable of surpassing experiment in accuracy.

But except on the simplest systems the computations proved to be complicated and laborious without yielding more than approximate results. Frustrated and repelled, many of the theorists began to turn to other problems.

Meantime, interpretative spectroscopy went through a rapid period of fruitful development. Here a good general theoretical framework was speedily set up, and continuing detailed computations were less essential. First atomic, then diatomic, spectra became relatively well understood through the efforts mainly of physicists and chemical physicists. Finally the novelty wore off, and the physicists began to turn to other fields. Polyatomic spectra remained, but were complicated.

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[1] This paper and the two following (5, 8) represent in part an elaboration, in part a condensation, of the paper presented at the Symposium on Color and the Electronic Structure of Complex Molecules which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago, Illinois, December 30 and 31, 1946.

World War II and the atomic bomb blasted away more of those still devoted to the fundamental and theoretical aspects of the structure and spectra of molecules, for these fields had little bearing on the immediate job of winning the war. Indirectly through the development of radar, however, the war has given delayed stimulus to the new field of microwave spectroscopy, now expanding with explosive rapidity. This is bringing again a considerable number of physicists into intimate contact with problems of polyatomic spectra and structure.[2] There is also a trend toward a long-needed mingling of knowledge and interests among specialists in various regions of the spectrum and in other fields which yield information on the structure of molecules.

There remains a vast vacuum in the complementary field of the quantitative application of quantum mechanics to the detailed understanding of the electronic structure of molecules. The further development of this field holds manifold possibilities for the better understanding and prediction of molecular properties and molecular structure.

Looking back at the first flush of enthusiasm for the application of quantum-mechanical calculations to molecular problems, it appears that too much may have been expected from pure theory. Perhaps if less had been expected, more progress could have been made,—by seeking and using just the right combinations of theoretical formulas and experimental information. Even in those days, such semiempirical blends were used with conspicuous success by, among others, Slater, Van Vleck, Eyring, and Pauling in this country, Hückel in Germany, and Lennard-Jones and Penney in England. Essential to the successful concoction of these appears to be a combination of the viewpoints and methods of the chemist and the physicist. I believe that the time is ripe for a new emphasis on the use of semiempirical methods in the application of quantum mechanics to molecular problems.

II. METHODS AND PROBLEMS

Let us review in outline the quantum-mechanical methods that may be used in understanding molecules and their properties, with particular reference to electronic spectra.

As an ideal goal, we might ask for the electronic eigenfunction and energy of every important molecule or class of molecules in its ground state and its important excited electronic states, as a function of all possible variations in the nuclear configuration, thereby also including all isomers. We should also like to know how the eigenfunctions and energies vary under the influence of force fields, particularly those resulting from the approach of other molecules. From such information, desired behavior and properties could be deduced by relatively simple calculations.

A. *Qualitative and quantitative methods: theory and experiment*

The complete attainment of such a goal would surely take decades, if not generations. It has taken centuries to apply Newton's laws to practical situations, and we are not through yet. In the application of quantum mechanics we have only started. While working toward our ultimate goal, less complete information will be very useful at first. This can be obtained by applying quantum mechanics in a variety of ways differing in their relative quantitativeness and in their relative content of pure theory and of empirical data.

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[2] **Written after attending the Symposium on Molecular Structure and Spectroscopy which was held at The Ohio State University, June, 1947.**

These applications in respect to the proportion of theory used may be divided roughly into four methods, all of which probably are worthy of much more extensive use than has yet been made of them:

(1) *The qualitative method:* judicious application of systematic qualitative and semiquantitative interpretations throughout the vast realm of inorganic and organic compounds in the solid, liquid, and vapor states.

(2) *The semiempirical method:* systematic theoretical computations of a relatively simple character, based on approximate wave functions of the molecular orbital or of the atomic orbital type, but making frequent use of empirical data as a substitute for, or even an improvement on, certain theoretical integrals. Empirical and semiempirical information likely to be useful for this purpose includes: frequencies, intensities, and other data from electronic spectra; excitation and ionization potentials, probabilities, and processes; dipole moments; thermal data; electronegativities derived from thermal data, dipole moments, and other sources; interatomic distances and bond angles from electron-diffraction, infrared, and microwave investigations; force constants and other information on bond properties from infrared and Raman spectra, including information on bond moments and polarizabilities as a function of internuclear distance, obtained from intensity measurements and other spectroscopic data.

(3) *The approximate theoretical method:* purely theoretical computations, using approximate molecular eigenfunctions of the molecular orbital or of the atomic orbital type.

(4) *The accurate theoretical method:* completely theoretical computations, using really accurate molecular eigenfunctions.

Computations of all types may be capable of very considerable extension with the use of the superpowerful computing machines now being developed.

B. The atomic orbital and molecular orbital approximation methods

Approximate theoretical methods for describing and computing electronic structures and spectra of molecules include, as is well known, the AO (atomic orbital) and the MO (molecular orbital) approximation methods. Here the word "orbital" is an abbreviation for "one-electron orbital eigenfunction." In simple molecules, each valence bond corresponds to a pair of electrons occupying a pair of linked AO's (AO method) or a single bonding MO (MO method). It is characteristic of the molecular problem that both of these methods, in different ways, are disappointingly far from exact in quantitative applications. More exact methods are available, but are far too complicated for application, at least for the present and probably for a long time to come, to any but very simple molecules.

The AO method fits well into the chemist's traditional conceptual framework of valence-bond structures. In its qualitative aspects, it is relatively simple for the ground states of molecules which can be described by a single definite set of chemical bonds, but loses this advantage in cases where "resonance" or "mesomerism" must be assumed.

The MO method is conceptually not as close to chemical valence ideas for ground states of molecules, but has certain other advantages. In particular, (*1*) the special and often arbitrary formulations used to describe the ground states of "resonating" molecules in the AO method disappear in the MO method, the MO description of such molecules being not different in kind or more complicated than for "normal" molecules; (*2*) the MO method usually is conceptually simpler and more transparent for the description of excited and ionized electronic states and electronic spectra than the AO method. Some of the most important cases where the MO method shows its characteristic advantages even for ground states are: molecules with polar bonds; molecules with double or triple bonds, including oxygen and all aromatic and conjugated molecules, molecules with trigonal conjugation as in BCl_3 or NO_3^-, molecules with cumulated double bonds, molecules with hyperconjugation, and so on; anomalous molecules like the boron hydrides; odd-electron molecules and radicals. The qualitative use (method 1 of Section II,A) of the MO method will be exemplified in the following paper on diborane and related molecules (5).

Since a large fraction of molecules showing color, or at least near-ultraviolet absorption, are molecules containing systems of double bonds, and in view of the general advantages of the MO method for excited electronic states, it is evident that this method should be particularly suited for understanding the electronic spectra of complex molecules. Moreover, as Hückel first showed, relatively simple yet significant semiempirical quantum-mechanical computations (method 2 of Section II,A) are feasible by an approximate form of the MO method.[3] These not only account remarkably well for the stability of aromatic and conjugated molecules, including free radicals, but also give a good account of the locations of their spectra. An apparent large discrepancy between the numerical value of the empirical parameter which fits the thermal data on resonance and conjugation energies, and the spectroscopic value of what theoretically ought to be the same parameter, is largely removed when a more refined treatment is used (7).

With the insertion only of an empirical correction factor (the need for which has been shown to diminish or disappear in cases where it has been feasible to use more accurate eigenfunctions), simple quantitative computations of the absolute absorption intensities of molecular spectra are likewise feasible. These can be used as an important aid in determining the nature of observed electronic spectra, or the geometrical configurations of the molecules to which they belong (6, 9, 10). The direction of polarization of the absorbed light can likewise be predicted theoretically, and can be observed in the case of molecules in crystals. Considerations of this sort have been used in the development of polaroid filters.

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[3] For a review see reference 4. At the present time Coulson and collaborators in England, among others, are carrying out important work in this direction. *Added in proof:* A valuable review on the MO method has just appeared (C. A. Coulson: Quarterly Reviews of the Chemical Society **1,** 144 (1947)); likewise, a valuable review on the use of the LCAO and the MO methods in interpreting electronic spectra (A. Maccoll: Quarterly Reviews of the Chemical Society **1,** 16 (1947)).

As above noted, qualitative and semiempirical quantitative applications of the MO method to problems of electronic structure and spectra have proved and should continue to prove fruitful. The AO method has also been applied in similar ways,[4] and its possibilities are worth exploring further; it may have special advantages for particular types of problems. Where possible, both methods should be used and the results compared.

Approximate computations of a more elaborate and more purely theoretical nature (method 3 of Section II,A) have also been carried out on the spectra of aromatic and dye molecules, particularly by the use of approximate wave functions of the MO and of the AO type, whose energies $\int \psi H \psi \, dv$ were determined (1, 2, 3,[5] 9[6]). Spectral frequencies and in some cases intensities were in this way computated quantitatively, and in rather good agreement with experiment. Except for the time-consuming nature of the computations by present means, this method shows considerable promise. Many of the integrals already computed in the work just mentioned could be taken over for use for other unsaturated molecules involving carbon or nitrogen atoms, thus bringing the effort required to moderate proportions. However, the results obtainable are limited by the roughness of the theoretical approximations used, and appear to be unreliable in the case of triplet states (7).

Hence the present writer is inclined to favor methods in which certain theoretically defined integrals are replaced by empirical parameters (method 2 of Section II,A). An illustration of the use of this method with MO approximate eigenfunctions will be given in the second paper following this one, which deals with the subject of twisting frequency and the barrier height for free rotation in ethylene (8).

III. THE FUTURE

In conclusion: There is at the present time a vast body of empirical data on the spectra of complex molecules. The data are, however, relatively unsystematic and poorly organized. Also, the rich possibilities (qualified by certain limitations) for their theoretical interpretation are not generally understood. This situation points to two important needs.

One is the production of an authoritative compilation of quantitative data on the spectra of pure compounds. In the case of absorption spectra, the need is for accurate maps of *absorption coefficient* against frequency, including systematic comparisons of a maximum variety of derivatives of important molecules. The charts of the American Petroleum Institute constitute an important step in the direction of such a program. These maps should also be extended as rapidly as possible to include the very rich vacuum-ultraviolet region.

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[4] *Cf.* Hückel (4), papers of Pauling and Wheland, and others.

[5] This interesting paper by Herzfeld and Sklar (3) on polymethine dyes contains also references to earlier papers.

[6] See Sklar (9) for review and references. It should be remarked here that the present writer does not fully subscribe to all of Sklar's methods and conclusions.

The second need is a more general knowledge and a more general application of the existing possibilities for understanding the various absorption peaks and emission spectra, in terms of the characteristic electronic energy levels of various groups or atoms and the changes in these by steric and other effects. The now largely empirical and often inaccurate attribution of particular peaks to particular molecular groups or situations can and should be replaced by an increase and diffusion of theoretical understanding of molecular electronic spectra, so that observation, diagnosis, and prediction can be smoothly and correctly coördinated. At the same time, other related optical properties, for example, refractivities and optical rotation, should be subjected to similar theoretical coördination, and the whole should be brought into line with a deeper understanding of the electronic structures and bond properties of molecules in their normal states.

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THE STRUCTURE OF DIBORANE AND RELATED MOLECULES[1]

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The history of the two geometrical models hitherto proposed for diborane (ethane-like or D_3 model, and bridge model) is briefly reviewed. It is pointed out that once the geometrical model is known, the electronic structure follows from quantum mechanics. The writer's previous MO (molecular orbital) discussion of the electronic structure of diborane in its normal and lower excited electronic states for the D_3 model is reviewed, and a parallel discussion is now given for the bridge model. In contrast to the D_3 model, the bridge model gives diborane in its normal electronic state a very neat closed-shell electronic structure in terms of MO's. Such a closed-shell structure is much easier to correlate with the spectroscopic and other facts than the open-shell structure required by D_3. AO (atomic orbital) discussions of the electronic structure of diborane, though equally as valid as MO discussions, are more complicated because they require the use of several resonating valence-bond structures in proportions which it is difficult to estimate. This is true for both geometrical models.

[*Added in proof:* A computation of the overlap integral between two $2p\pi$ boron atom AO's shows that this is remarkably large, making it probable that boron can form strong double bonds even at single-bond distances. This gives added support to the bridge model for diborane and to Pitzer's proposed structures for the higher boron hydrides, and helps explain the stability of the boron trihalides and similar compounds.]

Methylated diboranes and other compounds related to diborane are discussed, and it is pointed out that all (including the aluminum halides, Al_2X_6) should be at least qualitatively similar to diborane in MO structure if the bridge geometrical structure is assumed. In terms of the LCAO MO approximation, it is clear that other atoms or radicals should in principle be capable of replacing the bridge hydrogens in diborane and related compounds. For example, a halogen atom $p\sigma$ orbital or a tetrahedral methyl group orbital should have qualitatively the same bridge-bonding capability as a 1s hydrogen orbital. The fact that $B(CH_3)_3$ is observed, and not $B_2(CH_3)_6$, does not disprove this, since it can be shown that boron trimethyl is strongly stabilized by trigonal hyperconjugation. A similar statement applies to the boron halides, where also the monomer, very strongly stabilized by trigonal conjugation, is observed. On the other hand, the observed existence of the dimeric forms in Al_2X_6, $Al_2(CH_3)_6$, and the like, may be attributed to lessened stability of the monomers in these cases, together with, in Al_2X_6, marked ionic stabilization of the bridge structure. Lower stability of the monomers is here expected because double-bond formation, hence all types of conjugation, are, as is well known, much weaker in other rows than in the first row of the periodic system. [*Added in proof:* An examination of band structures in new infrared spectrograms by W. C. Price in this Laboratory shows unambiguously that the bridge model of diborane is the correct one.]

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[1] The material in this paper was mentioned in general terms in the abstract of the paper prepared for presentation at the Symposium on Color and the Electronic Structure of Complex Molecules, which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago, Illinois, December 30 and 31, 1946, but it was not discussed in the talk given at the Symposium.

I. GEOMETRICAL MODELS AND ELECTRONIC STRUCTURES

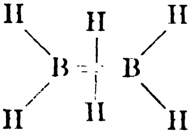
The boron hydrides, with their well-known electron deficiencies, furnish examples of the relative simplicity of MO as against AO descriptions when the AO method requires the use of resonating structures. Let us consider diborane as the simplest representative of these molecules.

There are two distinct questions: (*1*) What is the *geometrical structure?* (*2*) What is the *electronic structure?* In the literature, various answers have been given to both questions, but usually without making a clear distinction between them.

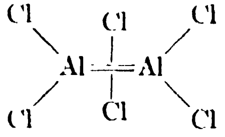
For the geometrical structure, two main alternatives have been proposed. One is the ethane-like model, which seems to have been generally taken for granted until the 1920's. The other is the bridge model, apparently first proposed by Dilthey in 1921. This was but little regarded until it was recently advocated (1940–45) by investigators in Russia, Germany, and England, and by Pitzer (1945) in this country (4, 5, 9, 12, 15). For brevity, the ethane-like geometrical model will in the following be called the D_3 model, after the point-group symbol describing the symmetry. In ethane, the symmetry may be D_{3d} (staggered form) or perhaps D_{3h} (eclipsed form); for our purposes these two variants are not greatly different, and can both be covered by the designation "D_3 model." The bridge model has V_h symmetry, like ethylene (*cf.* figure 1).

With neither model is a simple AO description of the electronic structure possible. A variety of sets of resonating structures have been proposed by various investigators. It seems clear that an adequate description would require a considerable number of minor resonating structures in addition to two or three major ones. Of special interest is Wiberg's proposal (1928, 1936) of an ethylene-like electronic structure with two of the protons embedded therein; Wiberg was not specific about the geometrical model. Wiberg also proposed a butadiene-like structure for B_4H_{10}.

Eistert (7) explicitly combined the bridge model with Wiberg's embedded-proton electronic structure, and used a similar description for the aluminum halides Al_2X_6, where the V_h model has been accepted for some time. Eistert proposed symbols such as:



and



Pitzer likewise coupled the V_h bridge model with an ethylene-like electronic structure. He also extended the idea to various higher boron hydrides, by combining it with the additional idea that the ethylenic electronic structures conjugate with normal $-\mathrm{B}\langle$ structures. Pitzer in a later paper (13) rejected the ethylene-like electronic structure for $Al_2(CH_3)_6$ and related compounds.

II. MO METHOD FOR THE D_3 MODEL

In the MO method, once the *geometrical configuration* of a molecule is specified, a definite *electron configuration* can usually be written down at once on the basis of qualitative or semiquantitative considerations derived from existing general knowledge of molecular electronic structures. Let us examine these MO descriptions, first for the D_3 model, then for the V_h bridge model.

The present writer in 1932–35, assuming the correctness of the D_3 model which was then rather generally accepted, discussed the MO electron configuration of diborane and certain of its corollaries for the properties of the molecule (10). Since $B_2H_6^{--}$ is isoelectronic with ethane, the electron configuration for the D_3 model of diborane must be the same as that of ethane, minus two electrons. This approach leads unambiguously to the electron configuration[2]

$$1s)^2 1s)^2 \sigma_g)^2 \sigma_g)^2 \sigma_u)^2 \pi_u)^4 \pi_g)^2 \qquad (1)$$

with three states $^3A_{2g}$, ^1E_g, $^1A_{1g}$, resulting from the half-filled π_g shell. On the other hand, in ethane the π_g shell is filled, giving a characteristically colorless, diamagnetic, saturated compound.

The predicted $^3A_{2g}$ normal state, which should make the substance paramagnetic, and the two low-lying excited singlet states, are closely analogous to the known normal and low excited states of oxygen, where also the last two electrons are in a half-filled π_g shell. However, π_g and π_u must be much closer together in energy in diborane than in oxygen, because in diborane the π orbitals are mainly B—H bonding.[2] As a result, the electron configurations . . . $\pi_u)^3\pi_g)^3$ and . . . $\pi_u)^2\pi_g)^4$ should give rise in diborane to a number of additional low-lying excited electronic states not found in oxygen.

Thus it is a definite and unescapable prediction that diborane, if the D_3 model is correct, must have a considerable number of singlet and triplet levels at low energies, i.e., between 0 and 2 or at most 4 or 5 ev., with the normal level probably a triplet and the substance therefore paramagnetic. Moreover, at least one strong and several weak electronic transitions among these levels, giving rise to electronic absorption bands in the infrared and/or visible or perhaps near ultraviolet, are predicted with certainty. By somewhat forced but not absurd assumptions (10), the normal state possibly could be diamagnetic.

Actually, diborane is diamagnetic, as was shown after the writer, assuming the D_3 model, had predicted it to be probably paramagnetic (10). Further, it has no electronic absorption between λ 12,000 and λ 2200, so that if the D_3 model is correct, the predicted low excited electronic levels must be very low indeed, and the corresponding electronic absorption must be in the infrared. Stitt's (14) investigation of the infrared spectrum indicated greater complexity than one would expect from the vibration spectrum alone for the D_3 model. The later work of Austrian and English investigators (4, 5, 9), however, shows fairly good agreement of the infrared and especially the Raman spectrum with what might be expected for the bridge model; nevertheless there are some discrepancies, including some unexplained infrared bands, though none of exceptional intensity.

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[2] The notation used here is that appropriate to a molecule with complete axial symmetry, like O_2 or CO_2. While this is not strictly accurate for C_2H_6 or B_2H_6, with its only threefold axial symmetry, it is essentially so for present purposes. The MO's are written in what the writer *now* believes to be substantially the correct order of diminishing ionization potential. The *main* bonding characteristics of the orbitals are: 1*s*, non-bonding *K* electrons of boron; first σ_g, B—B bonding; second σ_g, and σ_u, B—H bonding (distributed over all six B—H bonds); π_u and π_g electrons, B—H bonding (distributed over all six B—H bonds). It is also of importance here that π_u is slightly B—B bonding and π_g slightly B—B antibonding; this causes π_u to be somewhat more tightly bound than π_g. See reference 10 for further details.

Summarizing, it is seen that the MO method, using little more than qualitative reasoning, predicts with certainty the existence of a number of low electronic levels for diborane if the D_3 model is correct. The facts, however, lend no substantial support to these predictions and thus tend to controvert the D_3 model, although its disproof appears at present to be by no means conclusive.

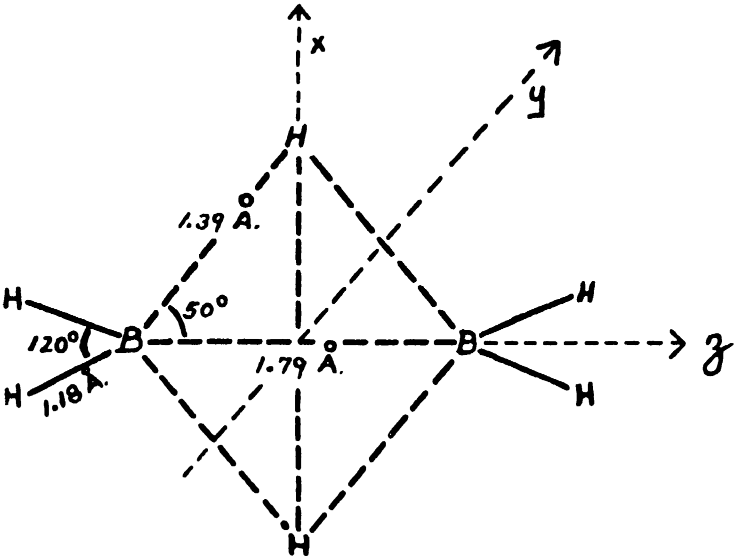


FIG. 1

III. MO METHOD FOR THE V_h BRIDGE MODEL

In view of the weight of evidence which seems to favor the bridge model (4, 5, 9, 12, 15), let us see what MO electron configuration this model requires. Although Pitzer has already indicated the general nature of the results, it appears worth while to go into more detail. (Pitzer says, "The molecular orbital picture of [the protonated double] bond is easily derived by breaking two protons off the carbon nuclei in ethylene and moving them to the indicated positions. It is readily seen that the same molecular orbitals are still appropriate, though now concentrated more around the protons. The general properties of this structural unit are just those expected of a double bond with two protons imbedded in it.")

According to Bauer's reinterpretation (1), in terms of the bridge model, of his electron-diffraction data, the structure of diborane is about as shown in figure 1. The symmetry of this model (V_h, or D_{2h}) is the same as that for ethylene. (To obtain ethylene, remove the two bridge hydrogens, replace B by C, and tighten up all the bonds.)

The MO electron configuration and electronic state may be written in a manner formally identical with that for ethylene, as follows:

$$\begin{array}{cccccccccl}
1s)^2 & 1s)^2 & a_g)^2 & a_g)^2 & b_{1u})^2 & b_{2u})^2 & b_{3g})^2 & b_{3u})^2, & {}^1A_g & \\
C & C & CC & H_2C,CH_2 & H_2C,CH_2 & H_2CCH_2 & H_2C\times CH_2 & CC, & \text{(ethylene)} & (2) \\
B & B & \overset{H}{\underset{H}{B\ \ B}} & H_2B,BH_2 & H_2B,BH_2 & H_2BBH_2 & H_2B\times BH_2 & \overset{H}{\underset{H}{B\ \ B,}} & \text{(diborane)} &
\end{array}$$

The symbols (except 1s for the two pairs of K electrons) are the usual MO symbols for symmetry V_h. Under each symbol is given a brief indication of the atoms which mainly are bonded by the MO in question. For ethylene, CC means mainly C—C bonding; H_2C,CH_2 means mainly C—H bonding, for all C—H bonds at once; H_2CCH_2 means H—C and C—C bonding in all bonds; $H_2C\times CH_2$ means C—C antibonding, but H—C bonding for all C—H bonds. For diborane everything is very similar, except that the two double-bond MO's a_g and b_{3u} now embrace the two bridge hydrogen atoms as well as the boron atoms.

In more detail, the forms of the MO's are qualitatively as follows. (Normalization factors are omitted, as are also certain coefficients which are not exactly equal; for example, $ss + \sigma_2$ means a linear combination, with more or less *unequal* coefficients, of the symmetry orbitals ss and σ_2.)

$$\begin{array}{rl}
\text{First } a_g & = \alpha(\sigma_1 + \sigma_1') + \beta(S'' + S''') \ * \\
\text{Second } a_g & = (ss + \sigma_2) + (\sigma_2 + ss)' \\
b_{1u} & = (ss + \sigma_2) - (\sigma_2 + ss)' \\
b_{2u} & = (s\bar{s} + \eta) + (\eta + s\bar{s})' \\
b_{3g} & = (s\bar{s} + \eta) - (\eta + s\bar{s})' \\
b_{3u} & = \gamma(\xi + \xi') + \delta(S'' - S''') \ *
\end{array} \qquad (3)$$

In equations 3, the single-primed symbols refer to the atoms of the right hand BH_2 group in figure 1; the unprimed symbols to the left-hand BH_2 group. The symbol σ_1 refers to an inwardly directed digonal boron hybrid AO, i.e., $2^{-\frac{1}{2}}(2s + 2p_z)$. The symbol σ_2 refers to an outwardly directed digonal AO, i.e., $2^{-\frac{1}{2}}(2s - 2p_z)$; σ_2 strongly overlaps and so gives strong bonding with the composite hydrogen orbital ss, which is formed by adding $1s$ orbitals of the two hydrogen atoms of the BH_2 group (i.e., ss means $1s + 1s$, with equal coefficients for the two $1s$ AO's). The composite hydrogen orbital $s\bar{s}$ (abbreviation for a subtractive combination of $1s$ orbitals of the two hydrogen atoms of the BH_2

group) is of such a form as to give strong overlapping and bonding with the boron orbital η (abbreviation for $2p_y$; for the y-axis, see figure 1). Finally, ξ means $2p_x$, the characteristic unsaturation AO which forms the second bond of the double bond; for the x-axis, see figure 1. (The foregoing all applies also to ethylene, if one substitutes "carbon" for "boron".) In the orbitals marked *, the symbols S'' and S''' refer respectively to 1s orbitals of the bridge hydrogen atoms in diborane; these disappear (and α, γ become 1 in a_g and b_{3u}) for ethylene.

The following two lowest *excited* MO's will also be useful (the second b_{3u} exists only in diborane, not in ethylene):

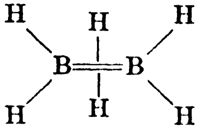
$$\begin{aligned}\text{Second } b_{3u} &= \delta(\xi + \xi') - \gamma(S'' - S''') \; * \\ b_{2g} &= \xi - \xi'\end{aligned} \tag{4}$$

It is notable that both these excited MO's should be fairly high in energy above the orbitals which are occupied in the normal state, *provided* the B—H binding and the B=B binding in the $\mathrm{B}\overset{\mathrm{H}}{\underset{\mathrm{H}}{\ }}\mathrm{B}$ bridge are both at least moderately strong. Under these circumstances, no infrared or visible electronic transitions would be expected. The second b_{3u} is B—B bonding but is antibonding with respect to the bridge hydrogens, while the b_{2g} is simply B—B antibonding.

Although there is a little uncertainty as to whether the MO's in the electron configuration given by expression 2 are all in exactly the correct energetic order, there is no question that this configuration, and its relation to that of ethylene, are correct if the V_h bridge model is correct. It is a very striking fact that the bridge model requires a diamagnetic, closed-shell electronic structure, with probably no low-lying excited levels and so no necessity of electronic absorption bands in the infrared or visible.

The electron configuration required by the bridge model provides eight electrons corresponding to the four normal B—H bonds. It also provides four electrons, in two orbitals, which do double duty in forming a B=B double bond and at the same time binding the two bridge hydrogens. From the forms of the two bridge MO's, it appears that the bridge hydrogens may be described as *bound to the double bond* rather than to the borons, though it would not be amiss to say that the two borons and the bridge hydrogens are all bonded together. The neatness of the arrangement is very striking if one sketches in to scale, on figure 1, the first a_g and the b_{3u} orbitals with forms as indicated by equations 3.

The foregoing results come out clearly and definitely using MO's, whereas in the AO method one must use a variety of resonating structures which give no very clear concept of the reasons why an unusual type of strong bond can be formed. The MO structure justifies to a considerable extent Pitzer's term "protonated double bond," but suggests that some such term as "four-atom bridge bond" would be preferable. This latter is especially true when one examines such geometrically similar bridged molecules as Al_2Cl_6 and probably $Al_2(CH_3)_6$ by the MO method. An appropriate symbol for the four-atom bridge bond would appear to be the following, similar to symbols used by Eistert[3] in 1942 and by Wiberg in 1944, after he had accepted the bridge model: namely, $\stackrel{\mid}{\underset{\mid}{=}}$, as for example in



(In this symbol it has of course to be understood that the plane of the normal B—H bonds should be perpendicular to the paper.)

IV. ULTRAVIOLET SPECTRUM OF DIBORANE

According to Blum and Herzberg (6), diborane gas shows weak continuous absorption beginning near λ 2200 and reaching a peak at about λ 1820. At the peak, if $I = I_0 e^{-kcl}$, with c in mols per liter and l in centimeters, k is about 25. The absorption falls to a minimum at λ 1700 and then rises gradually to beyond λ 1550 ($k \geq 50$ at λ 1550). The absorption is accompanied by rapid photochemical changes.

The λ 1820 peak is so weak that it may reasonably be attributed to a forbidden electronic transition. If the bridge model is correct, the most plausible identification is with the transition of an electron from the normal bridge MO b_{3u} (*cf.* equations 2 and 3) to the second, bridge-antibonding b_{3u} (*cf.* equation 4). Another possibility is a transition from the b_{3g} to the second b_{3u} MO. Both are forbidden transitions. They have no analogues in the ethylene spectrum, in partial disagreement with Pitzer's statement (12, p. 27, item 6) that the electronic energy levels and spectra are very similar to those of ordinary double bonds.

The transition from the first b_{3u} to the excited b_{2g} of equation 4 is one which definitely should be intense, being analogous to the very intense $N \rightarrow V$ ($b_{3u} \rightarrow b_{2g}$) transition in ethylene, with peak intensity at λ1630. Evidently the peak of this transition must lie below λ 1500.

If the bridge model is correct, the surprisingly large interval between the normal electronic level of diborane and the first observed singlet excited levels can only be explained if the two b_{3u} MO's—normal and excited—differ greatly in energy. (The peak at λ 1820 corresponds to 6.8 ev.) This requires that the first b_{3u} contribute very strongly to binding the bridge hydrogens.

V. WORK IN PROGRESS[4]

Work is in progress at this laboratory on the investigation of the infrared, ultraviolet, and vacuum-ultraviolet spectra of diborane. The infrared spectrum between 1 μ and 15 μ has been remapped by W. C. Price. This will permit a review of the conclusions which have been drawn from Stitt's infrared data.

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[3] See references 5, 7, 9, and 15 for discussion and references. Pitzer and Gutowsky (13) disagree with the bridge structure for dialuminum hexamethyl. *Added in proof:* However, R. E. Rundle (J. Am. Chem. Soc. **69**, 1327 (1947)) gives strong arguments against the structures proposed in reference 13.

[4] As of June, 1947. This work is being assisted by Office of Naval Research Contract N6ori-20, T.O.IX.

Comparison with the spectra of isotopic diboranes, in particular B_2D_6, which is in course of preparation in Professor H. I. Schlesinger's laboratory, offers good prospects for a final decision between the D_3 and V_h models, or the possible arrival at some other model.[5]

VI. BOND DISTANCES

The electrons in the first b_{3u} MO correspond to the π bond of the B=B double bond as well as being bridge-hydrogen bonding. The first a_g MO, whose electrons correspond to the σ bond of the B=B double bond, is also presumably strongly bridge-hydrogen bonding as well as B—B bonding. It might, however, be questioned whether these conclusions are in harmony with the approximately 1.79 A. B—B distance (see figure 1). This distance is approximately equal to the B—B distance corresponding to Pauling's single-bond radius (0.88 A.) for the boron atom. Thus one might question whether the observed distance is small enough for an effective B=B double bond.

In possible answer, the following points appear relevant: (*1*) The electron-diffraction value for the B—B distance is not very accurately known. (*2*) The form of the bridge MO's is such that strong bridge bonding B—H—B may be present even if the B—B distance is somewhat large and the direct B—B bonding rather weak. (*3*) In boron and carbon, the effective mean nuclear charge of the field in which $2p$ electrons move should be somewhat smaller than that for $2s$ electrons. In boron, this difference should be more pronounced than for carbon. Hence, since the ξ AO's (*cf.* equations 3, 4) are pure $2p$ with no $2s$ admixture, and since the size of an AO is inversely proportional to the effective nuclear charge of the field in which the electron moves, the second bond of a double bond formed by a boron atom may become fairly strong at a surprisingly large distance.

[*Added in proof:* A subsequent calculation of the overlap integral S between two $2p\pi$ Slater AO's for nuclear charge $Z_{ef} = 2.6\,e$ (Slater's effective value for boron), on centers 1.79 A. apart, gives $S = 0.23$. Assuming B^- AO's, with $Z_{ef} = 2.25$ (a case which is of interest since the boron atoms in diborane certainly have some excess negative charge), the value $S = 0.36$ is obtained. Thus the value of S for the π-π bond in diborane is as large as in ethylene, where $S = 0.27$, using Slater AO's. Since degree of overlap of valence AO's is recognized to be closely correlated with bond strength, this result indicates that 1.79 A. is not too large for strong B=B bonding. It also suggests that at its normal double-bond distance, boron should form remarkably strong double bonds. Further, it gives strong support to Pitzer's proposed structures for the higher boron hydrides, since it indicates that these structures would be strongly stabilized by conjugation of $2p\pi$ AO's on the various boron atoms, occupied by borrowed electrons; without unusual strength of π-π bonds at single-bond distances, it would be difficult to understand how such conjugation could be effective. The stability of trigonal conjugation in the boron trihalides, boric acid, and other compounds is also made more understandable.]

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[5] *Added in proof:* Subsequent examination of the new infrared data has shown unambiguously that the bridge model is correct: see W. C. Price, Letter to the Editor, J. Chem. Phys., August, 1947.

VII. RELATED COMPOUNDS

As is well known, several partially methylated diboranes are known, but none with more methyl groups than $B_2H_2(CH_3)_4$. This suggests that hydrogen atoms, but not methyl groups, can take bridge positions. However, there may be another reason. As is well known, the halides BX_3 (X = F, Cl, Br, I) and similar compounds do not form dimers. Nevertheless, in the corresponding aluminum compounds, the dimers Al_2X_6, with bridge structure, are the stable forms. The bridge structure is also accepted for $Al_2X_2(CH_3)_4$, and is plausible too for the fairly well established molecule $Al_2(CH_3)_6$ (see footnote 3, p. 213).

Examination and visualization of the forms of the diborane a_g and b_{3u} bridge MO's of equations 3 reveal no good reason why a tetrahedral (sp^3 hybrid), or approximately tetrahedral, carbon AO of a methyl group could not take the place of a hydrogen 1s AO (S'' or S''' of equations 3) in forming a bridge. It may be that the bridge bond so formed would be somewhat weaker (although even this does not appear obvious), but there appears to be nothing in the requirements of the bridge arrangement that would be detrimental to the strengths of the three C—H bonds of CH_3, while at the same time a tetrahedral or other σ-type carbon AO appears to be favorably shaped to show good bonding with the boron AO's in a_g and b_{3u} bridge MO's. A σ-type carbon AO apparently should be able also to act in a similar capacity in $Al_2(CH_3)_6$ with bridge structure.

Why, then, is $B(CH_3)_3$ found instead of $B_2(CH_3)_6$? As is well known, the boron halides, which are planar molecules, are strongly stabilized by a form of conjugation which may conveniently be called *trigonal conjugation*. The most striking empirical evidence of this, as Pauling pointed out, is to be found in the abnormally small B—X distances. The same phenomenon occurs in NO_3^-, CO_3^{--}, $B(OH)_3$, and similar entities. It results from the interaction of the excess π electrons of the outer atoms with the vacant π orbital on the central atom. The resulting stabilization is evidently so great that dimers B_2Cl_6 and so on are not formed, even though chlorine $p\sigma$ AO's should be capable of serving as bridge links (the argument is the same as that given above for σ AO's of methyl carbon atoms).

A consideration of the electronic structure of $B(CH_3)_3$ by MO methods shows that *trigonal hyperconjugation* should stabilize this molecule very considerably. A rough semiempirical MO computation, somewhat similar to that for the perpendicular form of ethylene, summarized in the following paper (11), indicates that this stabilization might amount to 1.5 or 2 ev. This conclusion appears to be in harmony with the B—C distance in $B(CH_3)_3$ and related compounds, as determined by electron diffraction.[6] Although Bauer (2, 3) concludes that the B—C distance in boron trimethyl (1.56 A.) is that corresponding to a normal covalent single bond, it is 0.09 A. smaller than the sum of Pauling's covalent radii (0.88 + 0.77 A.); and, since there is some form of conjugation or strong hyperconjugation in most of the boron compounds whose interatomic distances have been accurately measured, there seems to be no sufficient reason to suppose that the normal single-bond covalent radius is much less than Pauling's estimated value. It seems likely, then, that the occurrence of exceptionally strong hyperconjugation in $B(CH_3)_3$, rather than any inherent unfitness of methyl to replace hydrogen in a bridge bond, is responsible for the non-existence of $B_2(CH_3)_6$.

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[6] See references 2, 3, and 8 for electron-diffraction studies of boron trimethyl and related molecules.

This conclusion is in harmony with the existence of $Al_2(CH_3)_6$, and the likelihood of a bridge structure for this compound.[3] In the case of the halides, the fact that Al_2X_6 bridge molecules are formed rather than AlX_3 may of course, be explained largely on electrostatic grounds; the bridge form could be understood as a purely electrostatic equilibrium structure built of Al^{+3} and X^- ions. An additional factor favoring the dimeric forms may, however, be the familiar fact that only the first-row elements form strong double bonds; hence all types of conjugation should be weakened in the aluminum compounds and, in particular, trigonal conjugation stabilizing the monomeric molecules AlX_3 should be much weaker than for BX_3. It also follows, of course, that Al=Al double bonding should contribute very little to the stability of Al_2X_6 or $Al_2(CH_3)_6$. Nevertheless, a set of MO's qualitatively describable by equations 3, even though strongly polar, may well be present in Al_2X_6 and especially $Al_2(CH_3)_6$; an analogue of the suggestion on π bonds in Section VI is here pertinent. It seems possible that in the halides the bridge structure is primarily ionic but is nevertheless appreciably reinforced by covalent bridge bonding similar to that in diborane. In addition, the π electrons of the halogen atoms should make at least a small contribution in stabilizing these structures.

Other molecules which may be similar in structure to B_2H_6 are known, for example, Ga_2H_6 (5, 9).

VIII. SUMMARY

The respective MO electron configurations required by the ethane-like and the bridge geometrical models of diborane are discussed, and their predicted consequences for the properties of diborane, including its electronic spectra, are stated and compared with available evidence. The evidence favors the bridge model, but is not conclusive.[5] The electronic structures of related compounds, including Al_2X_6, are briefly discussed. It is pointed out that methyl groups should be able to assume bridge positions in derivatives of diborane and similar compounds. It is pointed out that boron trimethyl must be stabilized by trigonal hyperconjugation, and this is used to explain the fact that it does not dimerize.

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THE TWISTING FREQUENCY AND THE BARRIER HEIGHT FOR FREE ROTATION IN ETHYLENE[1]

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By the use of the semiempirical LCAO MO method the variation of the energy of the ethylene molecule, on twisting the plane of one CH_2 group relative to that of the other about the C=C axis, has been computed for each of four important electronic states, and also for the normal state of the ionized molecule. Three empirical parameters were used in the computations. Finally, estimated corrections for electronic interactions were made to the computed curves. The computations were made for each of several plausible sets of values of two of the parameters (those which govern the computed extent of hyperconjugation). For the third parameter, the bond integral β, a value -3 ev. taken from the ultraviolet spectrum was used. It is concluded that the 90°-twisted form of the molecule is more stable by about 1 ev., as a result of hyperconjugation, than it would otherwise be. An important and probably fairly reliable conclusion from the computations is that the potential curve for twisting is nearly a parabolic one, probably with slight *positive* anharmonicity; there are indications of support for this last point in the spectroscopic data. The computed frequencies and barrier heights show reasonable agreement with the most probable observed values. However, we do not wish to stress this agreement so much as the value of the computations as a step toward a better understanding of the possibilities and difficulties of the semiempirical LCAO MO method, and toward the possible determination of a reliable set of empirical parameters for use in other computations.

I. PURPOSES AND METHOD

Some computations made recently on the ethylene molecule furnish an interesting example of the use of the LCAO[2] molecular orbital method in its semiempirical form (*cf.* second preceding paper (7)). The purpose of the computations was twofold. The *first purpose* was to obtain information about the energy of the molecule in several of its important electronic states, not only for the normal planar geometrical configuration but also for configurations with the planes of the CH_2 groups twisted through various angles relative to each other; and, a corollary to this, to obtain information about the twisting frequency, and about the barrier height for thermal *cis-trans* isomerization. Such computations by the semiempirical method require the use of certain parameters for which reasonable values can be assumed in harmony with empirical

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[1] Abstract of material presented at the Symposium on Color and the Electronic Structure of Complex Molecules which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago, Illinois, December 30 and 31, 1946. A complete paper will be prepared for publication elsewhere at an early date.

This work was assisted by Office of Naval Research Contract N6ori-20, T.O.IX.

[2] Linear combination of atomic orbitals.

evidence. The present computations were carried through for each of several alternative sets of values of such parameters, chosen within a reasonable range based on previous experience. The *second purpose* of the computations, then, was to compare the results with further experimental evidence, in the hope of narrowing the range of choice of the parameters used, as a step toward an ultimate goal of a single consistent set of parameters suitable for use in computations on other molecules by the semiempirical LCAO MO method. Space here does not permit a discussion of the various limitations and qualifications that must be placed on the hope of attaining such a goal. The work here reported may perhaps best be regarded as an exploratory effort toward a determination of the feasibility of reaching a goal such as that stated.

The point of view used in any MO method is to regard the electronic structure as consisting of a set of electrons each occupying a definite MO (molecular orbital), commonly with two electrons of opposite spin in each MO. Each MO is in principle an eigenfunction of a one-electron Schrödinger equation. The appropriate Schrödinger equation is that for an electron moving in the electric field (i.e., the Hartree self-consistent field) due to all the other electrons and the nuclei.

In the LCAO MO method, the MO's are approximated by setting up linear combinations of known AO's (atomic orbitals) of the atoms concerned. The coefficients in these linear combinations are partly, or sometimes wholly, determined by the symmetry of the molecule. In our example of twisted ethylene, they are partly determined by the symmetry and partly by the solution of certain secular equations into which enter some of the semiempirical parameters already mentioned.

At the same time, the *energy* for each MO is determined from the solutions of the secular equations, with the introduction of one more semiempirical parameter. The total energy of the molecule is obtained, roughly, by adding the *orbital energies* (that is, the energies of the various occupied MO's), counted once for each occupying electron. To obtain the total energy more accurately, allowance must be made for the specific energies of interaction between electrons.

In the present work, a semiempirical computation has been made of the MO orbital energies for the *last six* of the sixteen electrons of ethylene, as a function of the *angle of twist* ϕ. For various trial sets of the semiempirical parameters, the orbital energy has been computed for several points in the range 0° to 90° and corresponding curves for the energy $U(\phi)$ have been plotted; the same curves apply to the range 180° to 90°, and the whole is repeated between 180° and 360°. It was then plausibly assumed that the total energy of the *first ten* ethylene electrons is essentially independent of the angle of twist. Finally, the forms of the integrals for the energies of interaction among the outer electrons were examined, and *estimates* made of the total contribution of these to the variation of the total energy with angle of twist. It was tentatively concluded that this contribution is a semi-order-of-magnitude smaller than that due to the variation of the orbital energy with ϕ.

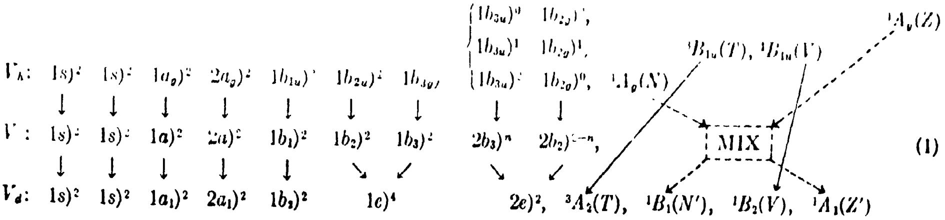
II. PENNEY'S WORK ON ETHYLENE

In 1934, Penney (12) discussed the structure of ethylene, both by the valence-bond AO method and by the LCAO MO method. He demonstrated the stability of the planar form for reasonable assumed values of certain relevant theoretical integrals in the AO method. He set up the secular equations for the LCAO MO method, but did not carry through as complete computations as we have done, and assumed values for the integrals which we believe now not to be empirically justified.[3]

Penney also showed in a second paper (13), that the frequency for twisting oscillations and the barrier height for 90° twisting are given by very simple expressions by the AO method, and from an observed value of the twisting frequency he obtained an empirical value of the double-bond π exchange integral, and also a value for the barrier height. These points will be referred to again later.

III. ELECTRON CONFIGURATIONS OF IMPORTANT ELECTRONIC STATES

In order to understand what happens to the electronic energy levels of ethylene when it is twisted from the planar to the *perpendicular form* (90° twist), it is necessary to consider simultaneously four electronic levels of the planar form, since all go over into states of a single electron configuration of the perpendicular form (5, 6).[4] These are the so-called N, T, V, and Z states of the planar form. Their electron configurations, and the way in which these are correlated with the electron configurations and states of the perpendicular form, can be expressed by the following scheme:


V_h: $1s)^2$ $1s)^2$ $1a_g)^2$ $2a_g)^2$ $1b_{1u})^2$ $1b_{2u})^2$ $1b_{3g})^2$
$\begin{cases}(1b_{3u})^0 & 1b_{2g})^2, \\ 1b_{3u})^1 & 1b_{2g})^1, \\ (1b_{3u})^2 & 1b_{2g})^0,\end{cases}$
$^1A_g(N)$
$^3B_{1u}(T)$, $^1B_{1u}(V)$
$^1A_g(Z)$
V: $1s)^2$ $1s)^2$ $1a)^2$ $2a)^2$ $1b_1)^2$ $1b_2)^2$ $1b_3)^2$ $2b_3)^n$ $2b_2)^{2-n}$,
MIX
V_d: $1s)^2$ $1s)^2$ $1a_1)^2$ $2a_1)^2$ $1b_2)^2$ $1e)^4$ $2e)^2$, $^3A_2(T)$, $^1B_1(N')$, $^1B_2(V)$, $^1A_1(Z')$

(1)

At the left are given the point-group symmetries (V_h for planar, V for partially twisted, V_d for 90°-twisted ethylene). The electron configurations follow, together with arrows to show how the MO's for one geometrical arrangement go over into those for another. Where two or more MO's belong to the same group-theory species, the one of lower energy is called 1, the next 2, and so on

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[3] W. G. Penney (12) set up the general LCAO MO secular equation for the complete set of MO's of ethylene, for various angles of twist and other distortions, but came to somewhat different conclusions from ours. Also, he concluded that the sixth-order secular equation for the π MO's does not factor for twisted ethylene, whereas we have shown that it does factor into two cubics, one for the b_2 and one for the b_3 MO's (*cf* our equation 3).

[4] On group-theory nomenclature and electronic structure in the perpendicular form, see especially reference 5.

(for example $1a_g$, $2a_g$). Detailed LCAO approximate forms and a description of bonding properties for the MO's of planar ethylene are given by equations 2–4, and the accompanying text, in the preceding paper on diborane and related compounds (8).

The most notable change on twisting to 90° is the coming together of the non-degenerate b_2 and b_3 MO's of untwisted or partially twisted ethylene into the degenerate $1e$ and $2e$ MO's of perpendicular ethylene. As a result, perpendicular ethylene contains a *half-filled shell* of $2e$ electrons, very similar to the half-filled π_g shell which occurs in the isoelectronic molecule O_2 and (for the D_3 geometrical model only) in the likewise isoelectronic B_2H_6 (8). (On the other hand, the electronic structure of planar ethylene is very similar to that for the bridge model of diborane.) This half-filled $2e$ shell gives rise to four electronic states, which can be shown[4] to be correlated as indicated in scheme 1 with the four states N, T, V, Z of planar ethylene. The states of perpendicular ethylene are here called N', T', V, Z', because a 50-50 mixing of the N and Z eigenfunctions takes place during the twisting to 90°.[4]

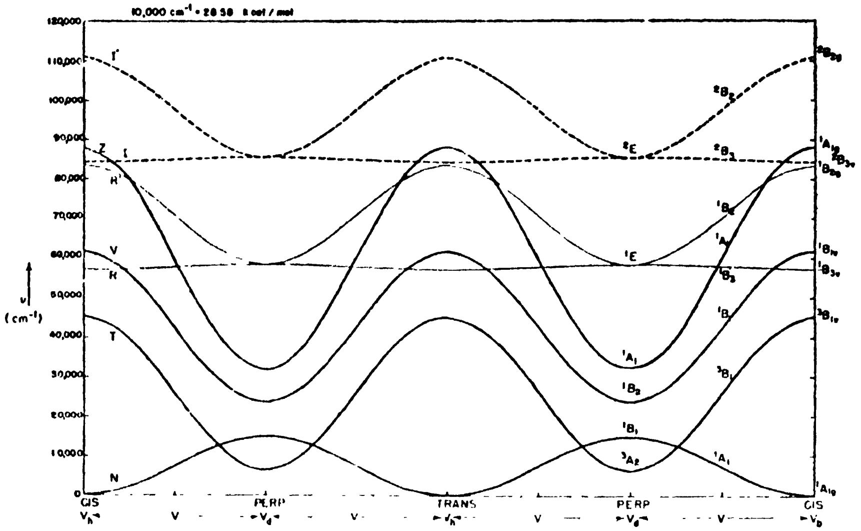

FIG. 1. Electronic states of ethylene molecule (*not based on present computations*). Variation in energy with angle of twist for the theoretically important electronic states N, T, V, Z of ethylene, and for certain excited states R, R' and ionized states I, I'. States N, T, V, R, I are observed states; Z, R', I' are related theoretically predicted states. The curves for N, T, V, R are based on an interpretation of available experimental data combined with qualitative theoretical considerations, as described by R. S. Mulliken (Rev. Modern Phys. **14**, 265 (1942)); the curve for I is drawn of the same shape as for R, in accordance with theory. These curves were drawn before the present computations were made; according to the latter, all the curves should be relatively higher for perpendicular ethylene.

Figure 1 shows qualitatively how the curves of states N, T, V, Z, also those of two other excited states R and R' and of two ionized states I and I', should vary on twisting the molecule. These curves were drawn before the present computations were made; according to the latter, the heights of the curves for perpendicular ethylene are somewhat greater.

As can be seen from an inspection of the forms of the MO's $1a_g$, $2a_g$, and $1b_{1u}$ of planar ethylene as given in equations 3 of the preceding paper, no important change in these MO's is to be expected during twisting. Thus it is reasonable to assume that the total energy of these and the K electrons does not change appreciably as a direct result of twisting. However, if the C=C bond should be lengthened as a result of twisting, the energy of these electrons would be somewhat affected. This point will be considered later; a preliminary check indicates that the effect is small.

We have then to consider just the *last six electrons*, those which occupy MO's which become $1e$ and $2e$ in the 90° form. This problem might be treated in either of two ways: (*1*) consider just the last two electrons, those which become $2e)^2$ in the 90° form, and assume that the next four electrons, which become $1e)^4$ at 90°, do not contribute much to the energy change on twisting; (*2*) consider the last six electrons together. In a computation parallel to the present one, following the approximate-theoretical method (7) in LCAO MO form, Parr and Crawford (11) are using the first of the above-mentioned two approaches. In the present paper we are using the second, following the semiempirical method in LCAO MO form

By considering all six outer electrons, we take into account the phenomenon of hyperconjugation. This is responsible in planar ethylene for an appreciable energy stabilization of the four next-to-outer electrons (10); and in 90° ethylene for a *further* stabilization of the molecule by strengthened hyperconjugation, involving both the four middle and to some extent the two outer electrons. The existence of hyperconjugation, partially offsetting the loss of bond strength in 90°-twisted ethylene, was first pointed out some time ago, though the word "hyperconjugation" was not then used.[4]

IV. ENERGY RELATIONS FOR NORMAL AND TWISTED MOLECULES

Given below is a comparative tabular outline of theoretical energy relations for the planar and the perpendicular forms of ethylene. Listed are energy formulas for states N, T, V, Z (or N', T', V, Z'), and also for the normal state I of the ethylene positive ion. The latter may be obtained in scheme 1 by removing one electron from $1b_{3u}$ of planar or from $2e$ of perpendicular ethylene. At the foot of the table are also stated (*a*) some additional theoretical relations, (*b*) some reasonable assumptions or estimates on the magnitudes of certain theoretical integrals or on relations between these, and (*c*) some observational data (6) which may be fed into the semiempirical method to supply numerical values for certain theoretical integrals, together with the empirical parameters or relations deduced using these.

In table 1, E represents the total energy of the given state. A represents the (unknown) total energy of the ten inner electrons,[5] which we assume does not vary appreciably with the angle of twist. I represents the total *orbital* energy of the four next-to-outer electrons. Each ϵ represents the *orbital* energy of one of the two outer electrons; ϵ_3^0 is the energy of the $1b_{3u}$ planar ethylene C—C bonding orbital of form $\xi + \xi'$, ϵ_4^0 is the energy of the corresponding C—C antibonding orbital $1b_{2g}$ of form $\xi - \xi'$, and ϵ_3^p is the energy of the nearly non-bonding $2e$ orbital of perpendicular ethylene. *It is I and the ϵ's which we have computed, as a function of the angle of twist ϕ.*

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[5] Plus certain Coulomb and exchange (J and K) interaction terms belonging to the six outer electrons, but whose sum it is reasonable to hope does not vary greatly with the angle of twist.

The values of the J's and K's, or of their variations with ϕ, have been estimated (see table 1) with the help of detailed theoretical formulas, or partly from experimental data, and also partly from theoretically computed integrals[6] available in the literature. The Coulomb integrals J and the exchange integral K_{34} are defined by

TABLE 1

Energy relations

PLANAR ETHYLENE	PERPENDICULAR ETHYLENE
Theoretical relations: $N: E = A^0 + I^0 + 2\epsilon_3^0 + J_{33}^0 - \gamma K_{34}^0$ $T: \quad + \epsilon_3^0 + \epsilon_4^0 + J_{34}^0 - K_{34}^0$ $V: \quad + \epsilon_3^0 + \epsilon_4^0 + J_{34}^0 + K_{34}^0$ $Z: \quad + 2\epsilon_4^0 + J_{44}^0 + \gamma K_{34}^0$ $I: \quad + \epsilon_3^0$	*Theoretical relations:* $T: E = A^p + I^p + 2\epsilon_3^p + J_{34}^p - K_{34}^p$ $N': \quad + 2\epsilon_3^p + J_{33}^p - K_{34}^p$ $V. \quad + 2\epsilon_3^p + J_{34}^p + K_{34}^p$ $Z': \quad + 2\epsilon_3^p + J_{33}^p + K_{34}^p$ $I: \quad + \epsilon_3^p$
$\gamma \approx K_{34}^0/(E_Z - E_N)$	$J_{33}^p > J_{34}^p$
Estimated: (a) $\gamma \approx 0.1$ (b) $J_{33}^0 + \gamma K_{34}^0 = J_{34}^0$ *Observational data (see reference 6):* (a) $E_V - E_N = 7.6$ ev. (b) $E_V - E_T \approx 2.2$ ev. (?) *Deduced from theoretical relations and these data:* (a) $K_{34}^0 = 1.1$ ev. (b) $\epsilon_4^0 - \epsilon_3^0 = 6.5$ ev. (c) $\beta_{spec} = -3.0$ ev.	*Estimated:* (a) $J_{33}^p - J_{34}^p = 0.6$ ev. (b) $K_{34}^p = 0.75$ ev. (c) No appreciable energy change due to stretching of carbon–carbon distance (d) (*Assumed*) $A^0 + J_{33}^0 - \gamma K_{34}^0 = A^p + J_{33}^0$ *Deduced from theoretical relations and above estimates and assumptions:* (a) $Q = E_{N'}^p - E_N^0$ $= (I^p + 2\epsilon_3^p) - (I^0 + 2\epsilon_3^0) - K_{34}^p$ $= (I^p + 2\epsilon_3^p) - (I^0 + 2\epsilon_3^0) - 0.75$ ev. (b) $Q_T \equiv E_T^p - E_N^0 = Q - (J_{33}^p - J_{34}^p)$ $= (I^p + 2\epsilon_3^p) - (I^0 + 2\epsilon_3^0) - 1.35$ ev.

$$J_{ij} \equiv \int \phi_i^2(\mu)(e^2/r_{\mu\nu})\phi_j^2(\nu)\, dv_\mu dv_\nu$$

$$K_{34} \equiv \int \phi_3(\mu)\phi_4(\mu)(e^2/r_{\mu\nu})\phi_3(\nu)\phi_4(\nu)\, dv_\mu dv_\nu$$

where ϕ_3 refers to the $1b_{3u}$ MO of planar ethylene or to the corresponding twisted

---

[6] Mainly from the computations of Goeppert-Mayer and Sklar on benzene (1), as extended by Griffing (1a). Reference 1 gives values of the necessary integrals for a C—C distance of 1.39 A. only, while reference 1a gives them for a range of distances, including the value 1.35 A. needed for ethylene.

MO, ϕ_4 refers to $1b_{2g}$ or the corresponding twisted MO, and μ and ν refer to two electrons at a distance $r_{\mu\nu}$ apart. The J's are known, from computations[6] by the approximate-theoretical LCAO MO method, to have values in the range 8–15 ev. The value of K^0_{34} is 1.1 ev. from experiment. Its value according to the theoretical method is[6] 4.0 ev.; the large discrepancy is an argument in favor of the present semiempirical method.

Details in partial justification of the estimated and assumed relations, involving A and the J's and K's and given in the lower part of table 1, will appear in the complete paper. These relations constitute the most doubtful part of the present work, but we feel moderately hopeful that we are approximately right in our estimates and assumptions about them, or at least that we are right in our conclusion that the variation of A and the J's and K's with ϕ is subordinate in importance to our computed variation of I and the ϵ's with ϕ. In any event, we believe that the present computations are instructive and suggestive.

V. THE SEMIEMPIRICAL LCAO MO COMPUTATIONS

We now outline the method used in computing I and the ϵ's as functions of ϕ. For the planar molecule, I^0 breaks up into the orbital energy of two electrons in the $1b_{2u}$ MO, plus that of two electrons in the $1b_{3g}$ MO. These and the orbital energies of the last two electrons, which occupy the $1b_{3u}$ or $1b_{2g}$ orbital (energies ϵ^0_3 or ϵ^0_4), can be computed separately, because in the planar model the MO's concerned all belong to different group-theory species.

The following equation (6, 9, 10) represents the orbital energies for the $1b_{3u}$ and $1b_{2g}$ MO's of planar ethylene in LCAO approximation (the upper sign gives ϵ^0_3, the lower ϵ^0_4):

$$\epsilon^0_{\substack{3\\4}} = \alpha \pm \beta/(1 \pm S) \tag{2}$$

where α is an atomic Coulomb integral giving the major part of the binding energy of the electron, β is the *bond integral* (9, 10), and S is the overlap integral $\int \xi\xi' dv$. The quantity α enters only as an additive constant, so that for our purposes it is unnecessary to determine its value. S is computed theoretically with sufficient accuracy, using approximate carbon atom $2p_x$ AO's (ξ means $2p_x$; see preceding paper (8) after equations 3).

Finally, β remains as one of our principal empirical parameters. An empirical value for β, which we call β_{spec}, is determined from observational spectroscopic data on ethylene in the manner indicated in the left-hand lower part of table 1. As shown there,

$$\epsilon^0_4 - \epsilon^0_3 = E_V - E_N - K_{34}$$

if we assume J^0_{33} approximately equal to J^0_{34}, as can be shown to be reasonable. K_{34} is approximately known empirically; then, from equation 2, we have

$$\epsilon^0_4 - \epsilon^0_3 = -2\beta/(1 - S^2)$$

from which is obtained our empirical $\beta_{spec} = -3.0$ ev. This empirical value is not necessarily the best, but its approximate correctness is indicated by the results of its use in other computations (6, 9, 10). It is to be hoped that an improved value will come out of a trial-and-error process of using it in various computations and checking the results against experiment.

When the molecule is twisted, the MO's occupied by the six outer electrons partially lose their symmetry, and now fall into just two group-theory species: namely, b_2 and b_3 (see scheme 1). The occupied MO's for the general case of an intermediate angle of twist are $1b_2$, $1b_3$, and $2b_3$, while $2b_2$ is also important for the excited states; for $\phi = 90°$, $1b_2$ joins $1b_3$ in belonging to $1e$ and $2b_2$ joins $2b_3$ in belonging to $2e$ (*cf.* scheme 1). It can be shown that $1b_2$, $2b_2$, and a third highly excited MO $3b_2$ are solutions of a cubic secular equation, while $1b_3$, $2b_3$, and a highly excited MO $3b_3$ are solutions of a second cubic secular equation.[3] The secular equation for the three b_2 MO's is given here in order to illustrate the empirical parameters involved; full details will be given in the complete paper. It is as follows. The secular equation for the b_3 MO's is similar, and involves the same parameters:

$$\begin{vmatrix} X - \delta & [\cos\tfrac{1}{2}\phi/(1+S)^{\frac{1}{2}}][S^*X - \beta^*] & [-\sin\tfrac{1}{2}\phi/(1-S)^{\frac{1}{2}}][S^*X - \beta^*] \\ [\cos\tfrac{1}{2}\phi/(1+S)^{\frac{1}{2}}][S^*X - \beta^*] & X - \beta/(1+S) & 0 \\ [-\sin\tfrac{1}{2}\phi/(1-S)^{\frac{1}{2}}][S^*X - \beta^*] & 0 & X + \beta/(1-S) \end{vmatrix} = 0 \quad (3)$$

Here X is an abbreviation for $\epsilon_i - \alpha$, and the three solutions of the equation give ϵ_2 (for $1b_3$), ϵ_3 (for $2b_3$), ϵ_6 (for $3b_3$) for any angle ϕ; ϵ_1, ϵ_4, ϵ_5 come from the other secular equation. The quantity S^* is an overlap integral which can be computed theoretically.

The quantities β, β^*, and δ are the *three empirical parameters* which are involved in our computation. The parameter β has already been discussed. The parameter β^* is a C—H *bond integral* associated with the interaction between an η carbon AO and an *ss* composite hydrogen orbital (see equations 3 of previous paper (8) and following text). *Both β and β^* are negative.* The parameter δ is a *relative electronegativity parameter*. Specifically, δ is the difference in Coulomb energy $\alpha_H - \alpha_C^{2p}$ between a $1s$ hydrogen AO and a $2p$ carbon AO, the latter being what is involved here (η is $2p_y$). It is expected to be *negative*, since hydrogen is *more* electronegative than carbon $2p$, even though it is *less* electronegative than an average (sp^3 hybrid) carbon AO.

In solving the secular equations, we have taken β as the unit of energy (10). The solutions depend only on β^*/β and δ/β. The value of β obviously enters only in determining the absolute values of the MO energies ϵ_i.

We have solved the secular equations for several values of ϕ ranging from 0° to 90°, for each of several sets of the adjustable parameters β^*/β and δ/β, as follows:

(A) β^*/β very large (*case of no hyperconjugation*)
(B) $\beta^* = 2\beta, \delta = 0$
(C) $\beta^* = 2\beta, \delta = \beta$ (4)
(D) $\beta^* = 1.5\beta, \delta = 0$
(E) $\beta^* = 1.5, \delta = \beta$

The various ϵ_i's were obtained, in units of β, for each parameter-set and for various angles. Adding up the ϵ_i's, each times the number of electrons in the corresponding MO, for each of the various states N, T, V, Z, I (see equations 1), and multiplying by $\beta = -3.0$ ev. in all cases, the total orbital energy of each state (aside from an additive unchanging constant) was obtained and plotted as ordinate against ϕ as abscissa.

Finally, these curves were corrected for the specific interelectronic interactions of the last two electrons. This was done by using certain relations, given in the second column of table 1 under the heading "Estimates", to determine the *differential* contributions, at 90° as compared with 0°, of these interelectronic interactions to the total energy. Having corrected the relative ordinates of the energy curves at 0° and 90° by this means (the corrections are a semi-order-of-magnitude smaller than the difference in ordinate between 0° and 90° based on the orbital energies alone), the final curves were drawn by assuming their ordinates to be everywhere proportional to those for the curves of orbital energy alone. We feel that this somewhat arbitrary procedure should not lead to any serious error for the conclusions drawn below.[7]

VI. THE POTENTIAL CURVE FOR TWISTING

Let us denote by $U(\phi)$ the curve of total energy E of state N as a function of ϕ. $U(\phi)$ is the potential-energy function for the twisting vibration ν_4 (Herzberg's notation) of ethylene. If we define

$$k \equiv (d^2U/d\phi^2)_{\phi = 0}$$

then

$$\nu_4 \text{ (in cm.}^{-1}\text{)} = (1/2\pi c)(k/m_H\rho^2)^{\frac{1}{2}} \tag{5}$$

as is easily shown, where c is the speed of light, m_H is the mass of a hydrogen atom, and ρ is half of the hydrogen–hydrogen distance in a CH_2 group. Let us adjust the additive constant in $U(\phi)$ so that $U(0) = 0$.

On plotting our $U(\phi)$ curves we find, *for all the different sets of parameters tried*, that all may be represented by expressions of the form

$$U(\phi) = \tfrac{1}{2}k\phi^2 + a\phi^4 + \cdots \tag{6}$$

with a small positive a. That is, $U(\phi)$ is *nearly parabolic but has a small positive anharmonicity*.

Of course equation 6 fails to hold close to $\phi = \pi/2$, where $U(\phi)$ has a maximum. Let us denote the barrier height, for a process of *cis-trans* isomerization by going over the maximum of $U(\phi)$, by Q; then

$$Q = U(\pi/2) \tag{7}$$

It is of interest to compare our computed Q values with those for a simple parabolic curve $U(\phi) = \frac{1}{2}k\phi^2$. For the latter, it is found that $Q = \pi^2k/8$. For all our computed curves, it is found that $Q > \pi^2k/8$. This is qualitatively just as if equation 6 were valid all the way to $\phi = \pi/2$.

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[7] As to possible further lowering of the curves owing to increased C—C distance for perpendicular ethylene (causing, among other things, a decrease in β), preliminary consideration indicates that this would amount to only 0.2 ev.

Our theoretically predicted positive anharmonicity is possibly of significance in connection with the fact that the weak but well-established infrared band at 800 cm.$^{-1}$ has been identified as ν_4, whereas in the Raman effect the frequency 1656 cm.$^{-1}$ has been identified as $2\nu_4$.[8] If both identifications are correct, they would correspond to a positive anharmonicity.

It is of considerable interest that our computed $U(\phi)$ curves are radically different from the potential curve of the cos 2ϕ form usually assumed (3). Again setting $U(0) = 0$, and defining k as above, the cos 2ϕ type of curve is given by

$$U(\phi) = \tfrac{1}{4}k(1 - \cos 2\phi) \tag{8}$$

For a given k—hence for a given ν_4—equation 8, which corresponds to a strong negative anharmonicity, gives a much smaller barrier height than a parabolic curve or, even more so, than our computed curves. The comparison is as follows:

$$\begin{aligned} \text{For equation 8: } Q &= \tfrac{1}{2}k \\ \text{For } U = \tfrac{1}{2}k\phi^2\text{: } Q &= (\pi^2/8)k \\ \text{For our } U \text{ curves: } Q &> (\pi^2/8)k \end{aligned} \tag{9}$$

A word here about the potential curve for our case A of relations 4, the hypothetical case of *no hyperconjugation*. For this case, with $\beta^* >> \beta$, the orbital energies of $1b_2$ and $1b_3$ should be independent of ϕ, and (aside from electronic interaction corrections) $U(\phi)$ should be given by the orbital energy of an electron pair in $2b_3$, alone. Again taking $U(0) = 0$, this is easily shown to be

$$U(\phi) = -2\beta/(1 + S) + 2\beta|\cos\phi|/(1 + S|\cos\phi|) \tag{10}$$

from which

$$Q = -2\beta/(1 + S) = 4.7 \text{ ev.}$$

This $U(\phi)$ function gives $k = -2\beta/(1 + S)^2$, or

$$Q = k(1 + S)$$

in which S is about 0.25.

The $U(\phi)$ curves for our cases B to E of relations 4 are lower than for case A, and give Q values 1–2 ev. lower than for case A, because hyperconjugation stabilizes perpendicular ethylene more than it stabilizes planar ethylene. But as already noted, the $U(\phi)$ curves for all the cases A to E give positive anharmonicity, and give Q greater than for $U = \tfrac{1}{2}k\phi^2$. As already discussed above, the $U(\phi)$ curves and Q values in all cases are lowered somewhat by the specific electronic interaction terms, but there seems to be no reason why this should change their shapes.

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[8] *Cf.* Herzberg (2). Although ν_4 (Herzberg's notation) is infrared forbidden, Herzberg suggests that Coriolis forces may explain its appearance; specific heats also indicate $\nu_4 \approx$ 800 cm.$^{-1}$ But see also Rasmussen and Brattain (14), who confirm the existence of the 800 cm.$^{-1}$ band but argue that 995 cm.$^{-1}$ may be ν_4.

However, as shown by Penney (12, 13), the AO approximation gives

$$U(\phi) = (3/4)I_2(1 - \cos 2\phi)$$

where I_2 is the major π electron exchange integral of the AO method. From this, he obtained also an expression for the twisting frequency ν_4, in terms of I_2 and the moment of inertia for twisting; and then from an empirical value $\nu_4 = 750$ cm.$^{-1}$ he obtained a value for I_2.

VII. THE TWISTING FREQUENCY

From plots of our final $U(\phi)$ curves corresponding to cases A to E of relations 4, the corresponding k and ν_4 values have been determined and are recorded in table 2. Similar plots have also been made for the ionized molecule in its normal state I (see table 1), and the corresponding ν_4 determined. In all cases we have taken $\beta = -3$ ev.

TABLE 2

Computed and observed twisting frequencies

	ν_4 (STATE N)	ν_4 (STATE I)
	cm.$^{-1}$	*cm.*$^{-1}$
Computed:		
Case A (no hyperconjugation)	892	660
Case B ($\beta^* = 2\beta$, $\delta = 0$)	836	Imaginary
Case C ($\beta^* = 2\beta$, $\delta = \beta$)	775	530
Case D ($\beta^* = 1.5\beta$, $\delta = 0$)	747	
Case E ($\beta^* = 1.5\beta$, $\delta = \beta$)	648	
Observed (2, 6, 14):		
Infrared, ν_4	800	
Specific heats	800	
Raman, from $2\nu_4$	828	
Ultraviolet, from possible $2\nu_4$		235 (145 for C_2D_4)

From other experience (6) we have reason to believe that the empirical parameters of case C are about right. However, there are some indications that the best values of $-\beta^*$ and $-\delta$ may *both* be a little smaller. This would not change the computed ν_4 very much. However, if $-\beta^*$ were *much* smaller, the energy order of $1b_{3g}$ and $1b_{3u}$ of planar ethylene would be reversed, in probable contradiction of the spectroscopic evidence.

The listed experimental ν_4 for state I is based on an ultraviolet frequency interval observed for a Rydberg state (6), which should be practically the same as the ionized state so far as the interatomic forces are concerned. The possibility of a very low computed ν_4 in agreement with that observed is shown by the fact that, in case B, ν_4 for state I is imaginary; that is, $U(\phi)$ has a maximum instead of a minimum at $\phi = 0$ (at larger ϕ it rises again). Thus it is reasonable to expect that for a suitable choice of the parameters β^* and δ, the experimental ν_4 could be matched. The observed isotope effect (C_2H_4 as against C_2D_4) for the ultraviolet frequency interpreted as ν_4 is *greater* than in the ratio $2^{\frac{1}{2}}$ predicted for ν_4. This could be explained by a very strong positive anharmonicity, a condition which also could probably be matched by suitable choices of the values of β^* and δ.

VIII. THE BARRIER HEIGHTS

The barrier height Q for *cis-trans* isomerization along the $U(\phi)$ curve for state N has already been defined; it is equal to $U(\pi/2)$. There is also another, lower, barrier height. It has been recognized for some time (5, 6) that state T should be somewhat lower in energy at $\phi = \pi/2$ than state N. We therefore define

$$Q_T \equiv E_T(\pi/2) - E_N(0)$$

According to table 1, we estimate that

$$Q_T = Q - 0.6 \text{ ev.}$$

Penney (13) gives $Q_T = Q - 0.2$ ev.

TABLE 3

Computed and observed barrier heights in electron volts

	Q	Q_T
Computed:		
Case A	3.3	2.7
Case B	2.9	2.3
Case C	2.5	1.9
Case D	2.3	1.7
Case E	1.8	1.2
Experimental:		
Thermal reaction rates (4)	(1.9)*	0.9†
Spectroscopic (ν_4 = 800):		
Equations 8, 9	1.0	
Our $U(\phi)$ (equation 9)	2.5	

* Complicated molecules.

† 2-Butene (also complicated molecules).

Magee, Shand, and Eyring (4) have analyzed data on the thermal *cis-trans* isomerization of various unsaturated compounds, which they interpret as giving in some cases Q, in others Q_T. Most of their data are on conjugated compounds, to which it is doubtful that the present computations would apply. In one case, however, that of 2-butene, a comparison of their empirical value of Q_T with ours should be in order. In table 3 our computed values for Q and Q_T for cases A to E are listed.

If Magee, Shand, and Eyring's Q and Q_T can be accepted for our case, they suggest that our estimated electronic interaction energy corrections, especially for state T, should be somewhat altered.

The "spectroscopic" Q's in table 3 depend on what form $U(\phi)$ is assumed to have. According to our computations, as well as the data of Magee, Shand, and Eyring, equation 8 gives much too low a Q. Penney (13), using equation 8 as given by the AO method, and using $\nu_4 = 750$ cm.$^{-1}$, got $Q = 1$ ev.

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ELECTRON LEVELS IN POLYATOMIC MOLECULES HAVING RESONATING DOUBLE BONDS[1]

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The first part of this paper discusses in general terms the electron levels of molecules in which resonance between double bonds occurs. It is pointed out that there exists, for every such resonance problem, an analogue of coupled mechanical oscillators or more generally of coupled A.C. circuits. The importance of the nodes is emphasized and it is made plausible that the energy increases with the number of nodes.

The second part is concerned with the effect of electronegative substitution on the absorption frequency connected with electron transitions. This effect is ascribed to the migration of electrons into the resonating system. The general formulas are given. It is shown that in polyenes the effect is very sensitive to the position of substitution; the shift can be to the red or to the violet.

In benzene, the shift is always to the red; in multiple substitution, the theory predicts approximate additivity which is confirmed by the data. The theoretical calculation of the frequency shift for fluorobenzene and phenol agrees fairly well with the facts.

I. GENERAL CONSIDERATION OF MOLECULES HAVING RESONANCE

A. Visible and ultraviolet absorption spectra of organic molecules

Such absorptions, at not too high temperatures, are due to transitions from the ground state to an electronically excited state. The problem arises therefore as to the nature of the excited states. In molecules which contain only single bonds, the excited states are closely related to the excited states of individual atoms. For most atoms occurring in organic molecules, the excited states lie so high that the first resulting absorption is in the far ultraviolet. This is the case in the simple hydrocarbons (30) (region around 1500 A.) and the alcohols (30) (region around 1600 A.). In the alkyl halides Price (20) has found a Rydberg series, corresponding to atomic excitation, but this absorption moves from 1600 A. for methyl chloride to 2900 A. for methyl bromide and 3600 A. for methyl iodide, corresponding to the shift in the ionization potentials of the halides.

We shall not consider these spectra further but turn to those associated with double bonds. A double bond consists of two parts, the normal single bond, in which the wave functions of two paired electrons—one from each atom—

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Several of the statements made in the abstract and the talk on the subject of the second half of this paper turned out later to be erroneous.

thoroughly overlap, and a so called π–π bond, made up of two π electrons or unsaturation electrons (Mulliken) or mobile electrons (Lennard-Jones), one in each atom. These electrons are approximately in unexcited atomic p functions, with the axis normal to the bond. The electron distribution (ψ function) is shown schematically in figure 1. The ψ function of a p atomic state has opposite signs on opposite sides of the nucleus, which fact is indicated in the figure by the shadowing, and therefore two arrangements are possible. At the left, the two functions point the same way and therefore add up in the central portion, where they overlap. Therefore, the electron density is relatively large between the two nuclei, and this negative charge provides the extra additional bonding between the nuclei (Penney (19)). On the right is shown the case where the two wave functions point in the opposite direction and therefore cancel out in the region where they overlap. In this case there is little negative charge between the two positive ions and the uncompensated repulsion between the positive ions makes this state antibonding.

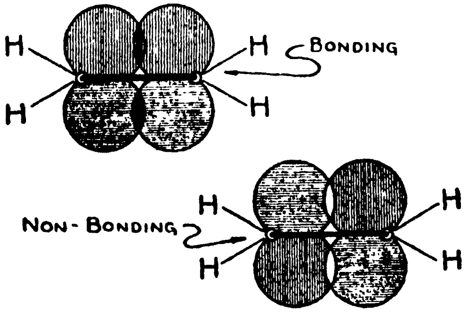


FIG. 1. π–π bond in ethylene

The atomic state with axis in the x direction is for carbon, nitrogen, oxygen, and fluorine a $2p$ state given by a hydrogen-like wave function

$$\psi = \frac{1}{4\sqrt{2\pi}}\left(\frac{Z}{a_0}\right)^{5/2} x\cdot\exp - \frac{Zr}{2a_0} \tag{1}$$

for sulfur, silicon, and chlorine the $3p$ state

$$\psi = \frac{1}{81}\sqrt{\frac{2}{\pi}}\left(\frac{Z}{a_0}\right)^{5/2}\left(6 - \frac{Zr}{a_0}\right) x\cdot\exp - \frac{Zr}{3a_0} \tag{1'}$$

where Z is the effective nuclear charge and a_0 the Bohr radius. The electron spins (of angular momentum $\frac{1}{2}\frac{h}{2\pi}$ each) may be antiparallel, so that they compensate and give a singlet state; this is the case for the bonding combination of wave functions. Or the spins may be parallel, when they add up and give a triplet state (three orientations), which occurs in the antibonding case.

The spectrum of an isolated double bond is experimentally (30) often still in the far ultraviolet (C_2H_4, 1750 A.; formic acid, 1550 A.; on the other hand acetone, 3300 A.). Most molecules giving absorption in the visible or near ultraviolet have conjugated double bonds, so that resonance phenomena become important, and this will be the subject considered from now on. To understand such resonance a mechanical analogue will be considered next.

B. Mechanical resonance

Consider four particles of equal mass (unity) arranged in a line, each of which is tied to its equilibrium position by a spring of force H. Then they can oscillate independently, and all have the same frequency ν, given by

$$4\pi^2\nu^2 = H \tag{2}$$

Now provide a weak spring h between any two neighbors. Then the whole system is coupled, and moves as a whole; there are four modes of vibration, shown with their frequencies in figure 2. Attention is drawn to the fact that the first mode of lowest frequency has no node, the next one has one node, the third one has two nodes, and the last one has three nodes. The results are derived from the equations of motion:

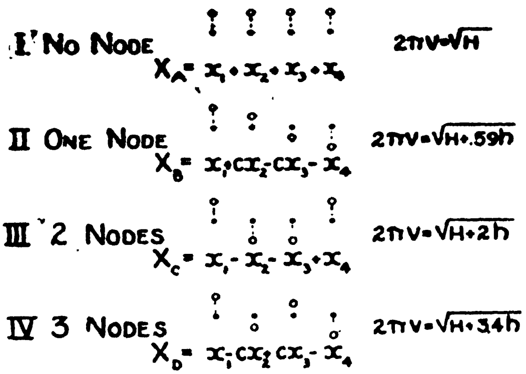

I No Node
$X_A = x_1 + x_2 + x_3 + x_4$
$2\pi\nu = \sqrt{H}$
II One Node
$X_B = x_1 + cx_2 - cx_3 - x_4$
$2\pi\nu = \sqrt{H + .59h}$
III 2 Nodes
$X_C = x_1 - x_2 - x_3 + x_4$
$2\pi\nu = \sqrt{H + 2h}$
IV 3 Nodes
$X_D = x_1 - cx_2 + cx_3 - x_4$
$2\pi\nu = \sqrt{H + 3.4h}$

FIG. 2. Modes of vibration for four particles of equal mass arranged in a line

$$\begin{aligned}
&\frac{d^2x_1}{dt^2} + Hx_1 + h(x_1 - x_2) = 0 \\
&\frac{d^2x_2}{dt^2} + Hx_2 + h(x_2 - x_1) + h(x_2 - x_3) = 0 \\
&\frac{d^2x_3}{dt^2} + Hx_3 + h(x_3 - x_2) + h(x_3 - x_4) = 0 \\
&\frac{d^2x_4}{dt^2} + Hx_4 + h(x_4 - x_3) = 0
\end{aligned} \tag{3}$$

These equations lead to the "secular equation"

$$\begin{vmatrix} H+h-\lambda & -h & 0 & 0 \\ -h & H+2h-\lambda & -h & 0 \\ 0 & h & H+2h-\lambda & -h \\ 0 & 0 & -h & H+h-\lambda \end{vmatrix} = 0 \tag{4}$$

which has four roots for λ, $\lambda = 4\pi^2\nu^2$. To each such root belongs one mode of vibration. However, the task of solving the equation is simplified by guessing at the form of the motion, e.g., for the first mode $x_1 = x_2 = x_3 = x_4$; if this is put into equations 3 it immediately leads to $\lambda = H$. Since the second and fourth mode shows $x_3 = -x_2$, the equations 3 are reduced to the form

$$-\lambda x_1 + (H + h)x_1 - hx_2 = 0$$

$$-\lambda x_2 + (H + 2h)x_2 - hx_1 + hx_2 = 0 \tag{5}$$

which easily gives for the second mode

$$\lambda = 4\pi^2\nu^2 = H + h(2 - \sqrt{2}) \tag{6}$$

$$\frac{x_2}{x_1} = \sqrt{2} - 1,\ x_2 = -x_3,\ x_4 = -x_1$$

and for the fourth mode

$$\lambda = 4\pi^2\nu^2 = H + h(2 + \sqrt{2}) \tag{6'}$$

$$\frac{x_2}{x_1} = -(\sqrt{2} + 1),\ x_2 = -x_3,\ x_4 = -x_1$$

The remaining third mode can also be easily found by setting $x_1 = x_4$, $x_2 = x_3$. Each of the four independent modes of vibration shown in figure 2 can be described by one "normal coördinate," which will be called here X_1, X_2, X_3, X_4. These normal coördinates are given by a linear combination of the momentary deflection of all four points,—these deflections being called here x_1, x_2, x_3, x_4. This statement is true not only if the points move in one of the four modes of vibration shown in figure 2, but also if they move in as general a way as is possible for the system, which general motion can be represented as a superposition of these four modes of vibration.

The equations are

$$\begin{aligned} X_1 &= b_1[x_1 + x_2 + x_3 + x_4] \\ X_2 &= b_2[x_1 + (\sqrt{2} - 1)x_2 - (\sqrt{2} - 1)x_3 - x_4] \\ X_3 &= b_3[x_1 - x_2 - x_3 + x_4] \\ X_4 &= b_4[x_1 - (\sqrt{2} + 1)x_2 + (\sqrt{2} + 1)x_3 - x_4] \end{aligned} \tag{6''}$$

$$b_1^2[1 + 1 + 1 + 1] = 4b_1^2 = 1$$

$$b_2^2[1 + (\sqrt{2} - 1)^2 + (\sqrt{2} - 1)^2 + 1] = (8 - 4\sqrt{2})b_2^2 = 1$$

$$b_3^2[1 + 1 + 1 + 1] = 4b_3^2 = 1$$

$$b_4^2[1 + (\sqrt{2} + 1)^2 + (\sqrt{2} + 1)^2 + 1 = (8 + 4\sqrt{2})b_4^2 = 1$$

If the system moves in one of the modes pictured in figure 2, all the X's except one are zero (e.g., if it moves in mode 3, X_1, X_2, and X_4 are zero).

Attention should be drawn to the fact that the coefficients given above are the ones which have been calculated previously in equations 6 and 6′. For the general case of a system of n coupled oscillators, one has n normal coördinates $X_1 \cdots X_n$, which are given by

$$X_s = \sum_j c_j^s x_j$$

where the coefficients can be calculated by methods similar to those employed above (see Appendix I).

Exactly the same equations as the ones discussed now are also valid for a system of electrical circuits without resistance, coupled capacitively. If there is, in addition, inductive coupling, the secular equation of the type of equation 4 is replaced by one of the type

$$\begin{vmatrix} H_{11} - S_{11}\lambda & H_{12} - S_{12}\lambda & \cdots & H_{1n} - S_{1n}\lambda \\ H_{21} - S_{21}\lambda & H_{22} - S_{22}\lambda & \cdots & H_{2n} - S_{2n}\lambda \\ \cdots & \cdots & \cdots & \cdots \\ H_{n1} - S_{n1}\lambda & H_{n2} - S_{n2}\lambda & & H_{nn} - S_{nn}\lambda \end{vmatrix} = 0 \qquad (4')$$

Here the S_{jj} are self-inductances and the S_{jk} mutual inductances.

C. Wave function and energy of resonating systems

In the case before us, one ignores generally the in-plane bonds and deals with the π–π bonds only. Consider now a group of two CH_2 and two CH radicals, ignoring the unpaired electrons which will form the three single bonds when the groups are brought together to form $CH_2{=}CH{-}CH{=}CH_2$. We direct our attention to the four unpaired p electrons, one in each atom, which will be involved in the π–π bond formation. As long as the four groups are far apart, the electrons have the same energy, so that we have four states of equal energy, one in each atom, or for the system as a whole, a fourfold degenerate state. If we now bring the groups closer, there will be interaction between the four states of equal energy, i.e., an effect analogous to coupling in the mechanical or electrical circuit case discussed above. The fourfold degenerate state will be split up, and instead of four states of equal energy we shall have in this case, four states with four different energies.

The amount of splitting will increase the larger the coupling, i.e., the closer the atoms come together. It is this splitting of degenerate states by resonance which is the subject treated here. In the case of n carbon atoms, the result of the split is n (or less) energy states. In a solid metal, which is built up of a very large number of like atoms brought together, the levels lie so close that one gets a practically continuous "conduction band."

The task now before us falls into two parts: (*1*) to find formally the correct wave function, and (*2*) to calculate the energy.

The wave function of the whole molecule is always built up—in the approximation in most frequent use—as a linear combination of wave functions of certain "elements" on which the theory is based. These elements are either valence-bond structures or the individual atomic wave functions. The atomic wave functions enter in all cases, either directly or indirectly, into the construction of the wave function of these "elements" of the theory. In every case, however, the unmodified wave functions of the π electrons in isolated atoms have been used. This in itself is surely inexact, since the presence of the other atoms acts as perturbation. If an atom is subject to a perturbing field which does not introduce new places of infinite potential energy, its perturbed wave function can always be represented exactly by a series development into unperturbed wave functions. But it does not seem quite clear how this should be done in a molecule. If one grants, however, the use of the unperturbed atomic wave functions, the question arises as to how to make up the wave function of the whole molecule.

Two different approaches are in use; both have a naive and a sophisticated form. The first method, the valence-bond or Heitler–London–Pauling–Slater (HLPS) method, uses as elements the different valence-bond structures of the whole molecule; then the proper wave functions are linear combinations of the wave function of these valence-bond structures, and the computation problem is to find the correct coefficients.

In the naive form, only non-ionic valence-bond structures (for neutral molecules) are considered, and usually only those of low energy. In the sophisticated form, ionic structures are included, but for neutral molecules no atom loses or gains more than one electron. That is so because only two π electrons with the same axis of the dumbbell can be in the same atom (they have to have antiparallel spins).

The molecular orbital method (Lennard-Jones–Mulliken–Hückel) considers one-electron orbitals of the whole molecule, made up linearly of the atomic π functions of all the atoms having such electrons. The resulting molecular orbital is then the wave function for an electron which is considered as running through the whole molecule. These one-electron molecular orbitals for the whole molecule are then treated in the same way in which atomic one-electron states are treated in an atom, e.g., in a lithium atom, one has one $1s$, one $2s$, three $2p$, one $3s$, etc. one-electron atomic orbitals. In the ground state of the lithium atom, the three electrons are located in the lowest possible states, not more than two to a state. The ground state of the lithium atom has therefore two electrons in $1s$ and one electron in $2s$. By analogy, the benzene molecule has six molecular orbitals; in the ground state there are two electrons in each of the three lowest states. Excitation consists in having one or more electrons transferred to higher orbitals.

In the naive valence-bond method, ionic states were excluded; in the naive molecular orbital method, the effect of repulsion between electrons on the wave function is not considered, and therefore, more than one π electron arrives "by accident" oftener at the same atom than should be the case. This can be partly remedied by complete antisymmetrization (6, 25) which, however, complicates the calculation greatly.

Assuming that the wave functions are known, the calculation of the energy is straightforward; however, in practice it might become impossible for large molecules, owing to the great number of terms in the expression. For fairly exact calculations with antisymmetrized molecular orbitals, the Wurster salts (5) and biphenyl (11) seem to present the limit attainable without calculating machines.

The problem which does present theoretical difficulties is that of finding the wave functions. The general problem of the proper wave functions for the electrons which form the π–π bonds is formally the same as for the electrons forming the single bonds. An excellent critical discussion of the methods used has been given by Van Vleck and Sherman (32; see also 33). The presentation in this section follows their discussion.

Actually it is not necessary to calculate the wave functions before one can get the energy values. One proceeds in the following manner: Write the compound wave function:

$$\Psi_s = \sum_j c_j^{(s)} \psi_j \tag{7}$$

Here Ψ_s is the wave function of the whole molecule (HLSP method) in the s^{th} state or the wave function of the s^{th} molecular orbital (MO method), while ψ_j is the wave function of the j^{th} valence-bond structure (HLSP) or of the π state in the j^{th} atom (MO).

The $c_j^{(s)}$ are coefficients, and their calculation would permit writing the wave function to be used.

If H is the Hamiltonian function of the whole molecule, one defines the numbers:

$$H_{kj} = \int \psi_k^* H \psi_j \, d\tau \tag{8}$$

$$S_{kj} = \int \psi_k^* \psi_j \, d\tau \tag{8$'$}$$

Then one can express the energy in general as a quadratic function of the c. If one now looks for the lowest possible energy state and for the next higher states with wave functions normal to that of the lowest state, one gets equations of the form

$$\sum_j c_j^s (H_{kj} - S_{kj}E) = 0 \tag{9}$$

which can only be solved if the determinant

$$\begin{vmatrix} H_{11} - S_{11}E & H_{1n} - S_{1n}E \\ H_{n1} - S_{n1}E & H_{nn} - S_{nn}E \end{vmatrix} = 0 \tag{10}$$

This provides the n energy values E_s directly, and when they are known, the c values can be found from equation 9.

Often the following approximation is made:

$$S_{jj} = 1 \qquad S_{kj} = 0 \qquad k \neq j$$

That means that the overlap between wave functions of neighboring valence structures or neighboring atoms is neglected. For the in-plane bonds, such a neglect cannot be justified. In π–π bonds, however, and for the molecular orbital method, the error is much smaller. The determinant is then simplified and takes a form on which much mathematical work has been done: namely,

$$\begin{vmatrix} H_{11}-E & H_{12}\cdots & H_{1n} \\ H_{21} & H_{22}-E & \cdots \\ \cdots\cdots & \cdots\cdots & \cdots\cdots \\ H_{n1} & H_{n2}\cdots & H_{nn}-E \end{vmatrix} = 0 \qquad (10')$$

It should be pointed out again that all the different energy values E_s found by solving equation 10 or 10′ arise from the resonance splitting of the same (if only like atoms are concerned) unexcited atomic p states, and the transitions considered here occur only between levels arising in this way from the same atomic level.

From the mathematical standpoint, the solution of such an equation as 10 or 10′, which might be of high order, gives trouble, while the wave functions are afterwards found by a straightforward but tedious calculation of determinants and minors. It is, however, more enlightening to reverse the process and consider first the task of finding the proper wave functions. The calculation of the energies—one for each wave function—is then straightforward, but can become in practice almost impossible owing to the large number of terms.

The task of finding suitable wave functions for symmetrical molecules can be shortened by group theory. However, group theory itself is rather complicated and can be replaced in some cases by inspection and inspired guess work. For this purpose, one first shows that for every problem of quantum-theoretical resonance, there is a mechanical or electrical analogue. Assume that one has a quantum problem which requires a solution of a secular equation

$$\begin{vmatrix} H_{11}-\lambda & H_{12}\cdots & H_{n1} \\ H_{21} & H_{22}-\lambda\cdots\cdots & \\ \cdots\cdots & \cdots\cdots & \cdots\cdots \\ H_{n1} & & H_{nn}-\lambda \end{vmatrix} = 0 \qquad (10'')$$

or, in short,

$$|H_{ij} - S_{ij}\lambda| = 0$$

The solutions λ are the energy values E of the states resulting from the resonance splitting.

The mechanical analogue consists of a system of n particles of unit mass. The j^{th} particle is tied to an equilibrium position by a spring of restoring force constant $H_{jj} + \sum_{k \neq j} H_{jk}$, and tied to the k^{th} particle by a spring of restoring force constant $-H_{jk}$. This mechanical system will have n independent modes of vibration. For each mode of vibration, the motion of the whole system can be expressed by a "normal coördinate" which is a linear combination of the motions of the individual particles. To each mode of vibration corresponds one wave function, made up linearly of the wave functions of the elements used (valence-bond structures or single atomic wave functions.) Numerically the same coefficients which appear in the equation expressing the normal coördinate by the coördinates of the individual mechanical particles appear also in the equation which connects the correct wave function with the wave functions of the structure elements.

If only neighboring particles are connected by coupling springs, i.e., if in the resonance problem only neighboring atoms interact, each mode of vibration will show "nodes." In the corresponding wave function, a node means that there is in the molecular orbital a change of sign between the two atomic functions of the neighboring atoms considered. If a node falls on an atom, the wave function of that atom does not appear in the particular molecular orbital. In general the mode of vibration of lowest frequency (the wave function of the lowest molecular orbital) will have no node. All possible numbers of nodes, up to a maximum n', will appear in *one* mode of vibration (one molecular orbital). If no degeneracy exists, that is, if no two modes of vibration have the same frequency (no two orbitals the same energy), n', the maximum number of nodes, is equal to $n - 1$, the number of particles minus 1, and each number of nodes between 0 and $n - 1$ occurs in one mode of vibration and only one. If degeneracy exists, there will be more than one mode of vibration having the same number of nodes, but they will be differently arranged in these different modes. The maximum number of nodes occurring will then be less than $n - 1$ (see Appendices II and III).

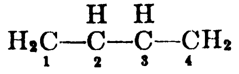
If it is possible to guess at the modes of vibration and, with the help of that guess, calculate with not too much trouble the modes of vibration and frequencies of the mechanical analogue as was done in Section I,B, this gives immediately the wave functions and energies (E instead of $4\pi^2\nu^2$).

This guessing is easier, the simpler and more symmetrical the mechanical system. For this reason, the method is particularly useful in the molecular orbital method, where the elements from which the correct wave function is built are the atomic one-electron p functions. These are the same for all carbon atoms and only different for other atoms like nitrogen, oxygen, and sulfur which might occur—usually at the periphery of the molecule. Most of the H_{ii} values are then equal.

D. Examples

This procedure for finding the wave functions will now be illustrated by some examples.

(*1*) *Butadiene* (*9*, *10*, *13*) (*figure 3*): There is a skeleton



$$\mathrm{\underset{1}{H_2C}-\overset{H}{\underset{2}{C}}-\overset{H}{\underset{3}{C}}-\underset{4}{CH_2}}$$

with one atomic π state and one π electron in each carbon atom (the latter are numbered 1, 2, 3, 4). It is assumed that only neighbors interact. The case is therefore exactly analogous to the mechanical example discussed in Section I, B and shown in figure 2. The wave functions of the molecular orbitals are, in order of ascending energy:

$$
\begin{array}{ll}
M_1\psi_1 = p_1 + p_2 + p_3 + p_4 & \text{No node} \\
M_2\psi_2 = p_1 + cp_2 - cp_3 - p_4 & \text{One node} \\
M_3\psi_3 = p_1 - p_2 - p_3 + p_4 & \text{Two nodes} \\
M_4\psi_4 = p_1 - c'p_2 + c'p_3 - p_4 & \text{Three nodes}
\end{array}
$$

Here p_j is the atomic π function of the j^{th} atom, M are normalization constants of the same character as the b's of Section I, B; the values of the constants c and c' are again $\sqrt{2} - 1$ and $\sqrt{2} + 1$. (For molecules of arbitrary n, the constants c can be best calculated by considering the analogous mechanical motion as a standing wave.) One sees that the wave function is (with respect to the center of the molecule) even or odd, depending on whether the number of nodes is even or odd. This is the background for Mulliken's statement that in polyenes the states are alternately even or odd.

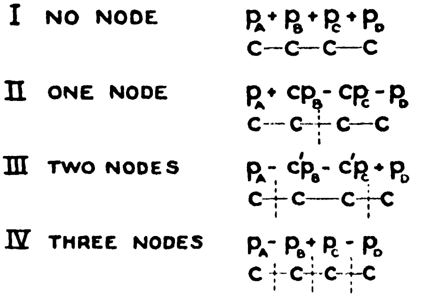


FIG. 3. Molecular orbitals for butadiene
$H_2C{=}C{-}C{=}CH_2$
A B C D

(*2*) *Benzene* (*6*, *25*) (*see figure 4*): There are six significant atomic π states, one in each carbon atom, and therefore six molecular orbitals must arise from the resonance splitting. The molecular orbital of lowest energy has no nodes; there is only one such state, and from symmetry the coefficients of all the atomic wave functions are the same.

$$M_1\psi_1 = p_1 + p_2 + p_3 + p_4 + p_5 + p_6$$

The largest number of nodes possible is three, and there is only one possible arrangement (the other imaginable arrangement would have the nodes go through all six carbon atoms, and then all coefficients would be zero and there would be no wave function). Therefore the molecular orbital of highest energy is:

$$M_6\psi_6 = p_1 - p_2 + p_3 - p_4 + p_5 - p_6$$

That leaves four states to be accounted for by one or two nodes, so that the orbitals having one or two nodes must either both be doubly degenerate or one triply degenerate and the other simple. As a matter of fact, both are doubly degenerate. The proper positions of the nodes are shown in figure 4, and the wave functions are:

$$\begin{aligned} \text{One node:}\quad & M_2\psi_2 = p_2 + p_3 - p_5 - p_6 \\ & M_3\psi_3 = p_1 + c(p_2 + p_6) - p_4 - c(p_3 + p_5) \\ \text{Two nodes:}\quad & M_4\psi_4 = p_2 - p_3 + p_5 - p_6 \\ & M_5\psi_5 = p_1 + p_4 - c'(p_2 + p_3 + p_5 + p_6) \end{aligned}$$

c and c' can again be calculated by considering the motion of the mechanical analogue as a standing wave problem.

As will be shown elsewhere, this method can be applied to rather complicated molecules.

E. The total number of molecular states

There is no direct connection between the number of valence-bond structures used in the Heitler–London–Pauling–Slater method and the number of one-electron molecular orbitals found by the MO method. On the other hand, the total number of molecular states arising, according to the MO method, is the same as the *total* number of valence structures.

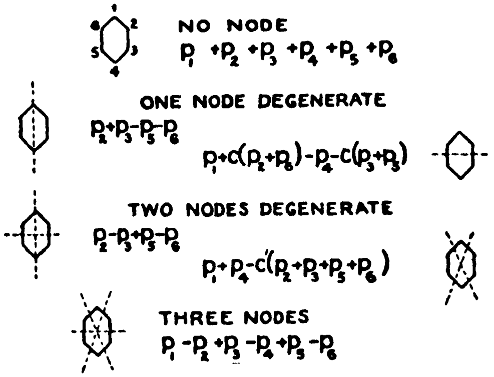

NO NODE
$p_1+p_2+p_3+p_4+p_5+p_6$
ONE NODE DEGENERATE
$p_2+p_3-p_5-p_6$
$p_1+c(p_2+p_6)-p_4-c(p_3+p_5)$
TWO NODES DEGENERATE
$p_2-p_3+p_5-p_6$
$p_1+p_4-c'(p_2+p_3+p_5+p_6)$
THREE NODES
$p_1-p_2+p_3-p_4+p_5-p_6$

FIG. 4. Molecular orbitals for benzene

While no general proof of this statement has been given, it will be illustrated below for butadiene. Of course, many of these molecular states are of no experimental importance because they lie higher than atomic excited states, or require the excitation of several electrons.

There are twenty valence structures of butadiene which are in the singlet state: namely, two non-ionic states, the usual one and one other, where one double bond connects the two inner, one the two outer carbon atoms; twelve singly ionized structures (four positions for the positive ion, and in each case three positions for the negative ion), with a double bond connecting the two neutral atoms; six doubly ionized structures $\left(\frac{4 \times 3}{2} \text{ positions for the positive ions}\right)$.

The molecular orbital method fills four molecular orbitals with four electrons.

This also gives twenty molecular states: namely, six states in which two orbitals contain two electrons each and the other two orbitals are empty (four orbitals available for the first electron pair, and in each case three orbitals then available for the second pair; but this counts each state twice). The ground state belongs to this group. Twelve molecular states in which one orbital is occupied by two electrons, two orbitals by one electron each, and one orbital is empty (any one of the four orbitals might be occupied by an electron pair, and in each case the empty orbital might be any one of the remaining three). The first excited state is in this group. Two states in which there is one electron in each orbital. These states differ only by the way the spins are paired.

No general formula for the total number of singlet states has been developed.

II. THE EFFECT OF SUBSTITUTION ON THE WAVE NUMBER OF ELECTRONIC TRANSITIONS

A. General considerations

Mulliken (15, 16, 17) has treated the effect of substitution on the electron levels of polyenes. If a hydrogen atom is replaced by a methyl group, Mulliken treats the latter as having the structure $C{\equiv}H_3$, so that a new double bond is added in the proper position (hyperconjugation). The results agree well with experiment.

Sklar (24) has considered the effect of substitution on the intensity of the forbidden transition at 2600 A. in benzene. He uses the molecular orbital method and draws attention to the consequences of the migration of charges into the benzene ring. His method, however, can also be used to explain the wavelength shift and to calculate it in first approximation. This is not limited to benzene, but can be applied to other molecules having resonating π–π bonds.

We shall call the resonating molecule or ion in which the substitution is made the "resonating system R" and the substituent X. We assume that there are no π–π bonds in the substituent. Call φ_j the j^{th} unoccupied orbital in the unsubstituted resonating system, W_j its energy (negative), ζ the occupied π orbital of proper orientation in the substituent, and W its energy. Call H_R the Hamiltonian of the unsubstituted resonating system, including the effects of all electrons contained therein, and H_X the Hamiltonian of the substituent after removal of one π electron. Abbreviate:

$$\omega_j = W_j + \int \varphi_j H_X \varphi_j \mathrm{d}\tau \qquad \omega = W + \int \zeta H_R \zeta \mathrm{d}\tau$$

$$2\rho_j = \int \varphi_j (H_R + H_X)\zeta \mathrm{d}\tau + S_j(W_j + W)$$

$$S_j = \int \varphi_j \zeta \mathrm{d}\tau \tag{13}$$

We assume $|\omega| > |\omega_j|$ (ortho-para-directing substitution).

Here ω_j, ω are the energies of the orbitals in R and in the substituent as modified by the Coulomb contribution of the other partner, S_j the overlap between resonating system orbital and substituent orbital, and ρ_j the exchange integral. If Λ_j^2 signifies the fraction of an electron from the substituent migrating into orbital j and b^2 the amount remaining, then the normalization condition is:

$$\sum_j \Lambda_j^2 + 2 \sum_j \Lambda_j b S_j + b^2 = 1 \tag{14}$$

The energy of an electron from the substituent, which is allowed to be distributed between the substituent and the unoccupied orbitals of the resonating group, is

$$\sum_j \Lambda_j^2 \omega_j + 2 \sum_j \Lambda_j b \rho_j + b^2 \omega$$

and the energy change due to migration is

$$U = \sum_j \Lambda_j^2 \omega_j + 2 \sum_j \Lambda_j b \rho_j + b^2 \omega - \omega \tag{15}$$

The summation goes over the unfilled orbitals of the resonating system. In equation 15 the term $2\Sigma\Lambda_k\Lambda_j \int \varphi_k H_X \varphi_j \, d\tau$ has been left out, for reasons given by Sklar. (We write Λ_j for Sklar's a_j and believe that Λ_j^2 is a better measure for migration than Sklar's λ_j^2.) If one minimizes U taking care of the normalization condition (expression 14), one finds, neglecting terms in Λ^3 and higher powers:

$$\Lambda_j = \frac{\rho_j - \omega S_j}{\omega - \omega_j} \tag{16}$$

This applies to unfilled states of the system, but is independent of what other states are filled. Introducing equation 16 in equation 15, one finds for the energy change in any state of the molecule:

$$U = \sum_j (\omega - \omega_j)\Lambda_j^2 \tag{17}$$

The terms have the opposite sign from the one which one would at first expect.

Consider now the shift in the wave number of a given electron transition. In the ground state of the resonating radical, all orbitals are filled up to a certain number n $\left(\text{in neutral molecules, } N = \frac{n}{2}\right)$. Therefore electrons from the substituent migrate into all the empty orbitals, $j > n$.

$$U_0 = + \sum_{j>n} (\omega - \omega_j)\Lambda_j^2 \tag{17'}$$

If now one electron is excited into the orbital $m > n$, this orbital (or half of it) is excluded from migration, but an orbital n has become free. Therefore, for the excited state

$$U_e = \Lambda_n^2(\omega - \omega_n) + \sum_{j>n} (\omega - \omega_j)\Lambda_j^2 - \Lambda_m^2(\omega - \omega_m) \tag{17''}$$

and the shift in wave numbers due to substitution has the value

$$\Delta\nu = \frac{1}{ch}(U_e - U_g) = \Lambda_n^2 \frac{\omega - \omega_n}{hc} - \Lambda_m^2 \frac{\omega - \omega_m}{hc} \tag{18}$$

$$\Lambda_j^2 (\omega - \omega_j) = \frac{1}{\omega - \omega_j} (\rho_j - S_j \omega)^2 \tag{18'}$$

In other words, the effect of substitution on the energy difference of an electron transition is due to the fact that, upon excitation, a migrating electron has been pushed out of the excited orbital but instead has been allowed to migrate into a previously filled, lower orbital.

The heat of ionization (taken positively) of an electron from the j^{th} orbital is changed through substitution by the amount

$$+ (\omega - \omega_j)\Lambda_j^2$$

B. Effect of the position of substitution and of the state of excitation

We limit ourselves here to substitution of a substituent X on a carbon atom, and assume that the distance between the substituent and the carbon atom is independent of the place of substitution. It is further assumed that this distance is the same in the ground state and in the excited state of the molecule. Overlap integrals between atoms which are not nearest neighbors are neglected. It is then possible to introduce some integrals which depend only on the nature of the substituent, but not on its position or the particular molecular orbital of the resonating system.

Write the wave function of the j^{th} molecular orbital of the resonating system in the form (see 32 and 33; here φ is used instead of ψ to indicate that φ is not the wave function of the whole substituted system):

$$\varphi_j = \sum_k c_k^{(j)} p_k \tag{19}$$

p_k being the atomic π function of the k^{th} carbon atom of the resonating system.

Then (see reference 13), if the substitution is made on the s^{th} carbon atom:

$$S_j = c_s^{(j)} S \tag{20}$$

$$S = \int p_s \zeta d\tau \tag{20'}$$

$$\rho_j = c_s^{(j)}[\rho' + \tfrac{1}{2}S(W + W_j)] \tag{21}$$

$$2\rho' = \int p_s(H_R + H_X)\zeta d\tau \tag{21'}$$

The assumption made in equation 21 is that the exchange energy integrals can also be neglected except between nearest neighbors.

Therefore one gets

$$\Lambda_j = c_s^{(j)} \frac{\rho' + \frac{1}{2}S(W - 2\omega + W_j)}{} \tag{22}$$

$W - \omega$ is independent of j and depends on the place of substitution only if R is an ion and H_R has a Coulomb part.

Therefore it is useful to introduce a further abbreviation:

$$\rho = \rho' + \tfrac{1}{2}S(W - 2\omega) \tag{23}$$

$$\Lambda_j = c_s^{(j)} \frac{\rho + \frac{1}{2}SW_j}{\omega - \omega_j} \tag{23'}$$

As long as the values of Λ are sufficiently small, the effects of more than one substitution ought to be additive.

C. Application to polyenes

If these formulae are applied to polyene molecules or methine dyes containing N carbon atoms, one has

$$\begin{aligned} c_s^{(j)} &= \frac{1}{M_j} \cos\left[\left(\frac{N+1}{2} - s\right)\frac{\pi j}{N}\right] \qquad j \text{ even} \\ &= \frac{1}{M_j} \sin\left[\left(\frac{N+1}{2} - s\right)\frac{\pi j}{N}\right] \qquad j \text{ odd} \end{aligned} \tag{24}$$

$$0 \leqq j \leqq N - 1, \; s \text{ running from 1 to } N$$

The last full orbital is $j = \frac{N}{2} - 1$; the first excited one is $j = \frac{N}{2}$ (N is even). Designate the former by the index g, the latter by the index e.

The ionization potential of the ground state is changed by

$$\frac{2}{3N}\left[1 - (-1)^s \sin \pi \frac{2s - 1}{N}\right]^2 \frac{(\rho + \frac{1}{2}SW_g)^2}{\omega - \omega_g} \tag{25}$$

and that of the excited state by

$$\frac{1}{N} \frac{\left(\rho + \frac{S}{2} W_e\right)^2}{\omega - \omega_e} \tag{25'}$$

Equation 25′ means that the migration into the excited orbital is independent of the position of the substituent. The question whether, upon substitution at the first carbon atom, the ionization potential of the ground state or that of the excited state is more affected depends on the question whether

$$\frac{2}{3}\left(1 + \sin \frac{\pi}{N}\right)^2 \frac{1}{|\omega_e - \omega_g|} \quad \text{or} \quad \frac{1}{\omega - \omega_e}$$

is larger (if the effect of SW, in the numerator is neglected).

The frequency shift is given by

$$\Delta\nu = \frac{1}{hcN}\left\{\frac{(\rho + \frac{1}{2}SW_g)^2}{\omega - \omega_g} \frac{2}{3}\left[1 - (-1)^s \sin \pi \frac{2s - 1}{N}\right]^2 - \frac{(\rho + \frac{1}{2}SW_e)^2}{\omega - \omega_e}\right\} \tag{25''}$$

Equation 25 has interesting consequences, which will be illustrated by an example. Abbreviate for the moment

$$\Delta\nu_1 = \frac{1}{hc}\,\frac{(\rho + \frac{1}{2}SW_g)^2}{\omega - \omega_g}\,\frac{2}{3N}$$

$$\Delta\nu_2 = \frac{1}{hc}\,\frac{(\rho + \frac{1}{2}SW_e)^2}{\omega - \omega_e}\,\frac{1}{N}$$

and apply the formula to $N = 6$. Then,

$$s = 1, 6 \quad \Delta\nu = \Delta\nu_1\left(1 + \sqrt{\frac{3}{2}}\right) - \Delta\nu_2$$

$$s = 2, 5 \quad \Delta\nu = -\Delta\nu_2$$

$$s = 3, 4 \quad \Delta\nu = \Delta\nu_1\left(1 - \sqrt{\frac{3}{2}}\right) - \Delta\nu_2$$

In general, the factor of the first term disappears if $\frac{N}{2}$ is odd, $\frac{N}{4} + \frac{1}{2}$ even, for $s = \frac{N}{4} + \frac{1}{2}$ and the corresponding atom $s' = N + 1 - s$. It is interesting that, if one sums up the wave-number shifts one gets by substituting in turn on all carbon atoms, one finds:

$$\Sigma\Delta\nu = \frac{1}{hc}\,\frac{(\rho + \frac{1}{2}SW_g)^2}{\omega - \omega_g} - \frac{1}{hc}\,\frac{(\rho + \frac{1}{2}SW_e)^2}{\omega - \omega_e}$$

D. Application to benzene and derivatives

(1) Experimental data

In this section the experimental data for the wave number of the 0–0 transition in the vapor state are collected (table 1), since only these can be used for comparison. Even these transitions contain, besides the electronic energy difference, the difference in zero-point energies in the excited and ground states, summed up over all vibration frequencies. It is hoped here that, while the zero-point energies themselves are affected by substitution, the differences might not be affected sufficiently to matter, so that the change in the wave number of the 0–0 transition upon substitution might be taken as change in the electronic transition.

(2) General theoretical considerations

The 2600 A. band arises in benzene if one electron is taken out of orbital 3 and transferred to orbital 5 (see Section I,D,(2)). The coefficients c of the atomic p function in the two orbitals are practically the same except for the normalization factors (called σ by Sklar). One has

$$c^g = \frac{1}{\sqrt{1.20}\cdot\sqrt{3}} = 0.53; \qquad c^e = \frac{1}{\sqrt{0.72}\cdot\sqrt{3}} = 0.68$$

One can then not say offhand that the shift must always be to the red. One can, however, expect that the substitutions which give a large red shift will also be effective auxochromes. Table 2 compares the red shift from table 1 with the values of Δf, the increase of transition probability for monosubstituted benzenes (24). A general parallelism is noted, except for the different positions of CH_3 and F.

(3) Additivity

It has been noted previously that for polysubstituted benzenes there should not be the pronounced dependence of the effect on the position of substitution which exists in the intensity (auxochromic effect), but that the red shift of substituents should be approximately additive. The data in table 3 are approximately in agreement with this statement.

TABLE 1

Monosubstituted benzenes

FORMULA	ν (0–0)	$\Delta\nu$	REFERENCE
C_6H_6	38,089		(30)
$C_6H_5CH_3$	37,484	−605	(30)
C_6H_5F	37,818	−271	(31)
C_6H_5Cl	37,052	−1037	(30)
C_6H_5Br	36,996	−1093	(30)
C_6H_5CN	36,516	−1573	(30)
C_6H_5OH	36,350	−1739	(30)
$C_6H_5NH_2$	34,034	−4055	(30)

TABLE 2

Comparison of red shift with auxochromic efficiency

COMPOUND	$C_6H_5CH_3$	C_6H_5F	C_6H_5OH	$C_6H_5NH_2$
$-\Delta\nu$ from table 1	605	271	1739	4055
$\Delta f \times 10^4$	12	100	170	200

There are, however, deviations: first of all, the position of substitution does make a difference; para substitution gives in general a larger red shift than ortho or meta substitution. It is consistent with this fact that the shift in 1,2,4-trichlorobenzene is larger than in 1,3,5-trichlorobenzene.

Two explanations for the effect of the position and for the deviation from additivity come to mind. The reason may be experimental, insofar as ν $(0 \rightarrow 0)$ is not the pure electron jump but contains also the difference in zero-point energies (Section II,D,(1)). On the theoretical side it may be noted that ω_j (equation 13) contains the effect of the Coulomb force, originating on the ionized substituent, on the benzene wave functions. For the di- and tri-substituted benzenes, this Coulomb term will depend on the number and on the relative position of the substituents. This fact will produce slight deviations from additivity for the red shift.

An additional reason for deviations from additivity is present if the migration is too large, so that migrations from different substituents react on each other. This effect is apparent in the amines.

(4) Theoretical calculation of the shift in monosubstituted benzenes

For this calculation, the following approximations are made: In the denominator of Λ (equation 22), namely, $\rho' + \frac{1}{2}S(W + W_j) - S\omega$, W is replaced by ω, i.e., $\int \zeta H_R \zeta d\tau$ is neglected, since the ring is neutral; W_j is replaced by its value from equation 13, therefore

TABLE 3

Polysubstituted benzenes

COMPOUND	ν (0–0)	$\Delta\nu$	REFERENCE
(1) Chlorobenzenes			
Chlorobenzene	37,052	−1037	(30)
o-Dichlorobenzene	36,230	−1859	(28)
m-Dichlorobenzene	36,186	−1903 average = 2036	(28)
p-Dichlorobenzene	35,743	−2346 $2 \times 1037 = 2074$	(28)
1,3,5-Trichlorobenzene	35,498	−2591	(28)
1,2,4-Trichlorobenzene	35,108	−2981 $3 \times 1037 = 3111$	(29)
(2) Mixed disubstituted benzenes			
p-Fluorotoluene	36,866	−1223 ($CH_3 + F = -876$)	(30)
o-Fluorotoluene	37,566	−523	(30)
Chlorotoluene	36,297	−1792 ($CH_3 + Cl = -1642$)	(30)
Bromotoluene	36,173	−1916 ($CH_3 + Br = -1698$)	(30)
(3) Methylbenzenes			
Toluene	37,484	−605	(30)
1,3,5-Trimethylbenzene	36,488	−1600 $3 \times 605 = 1815$	(29)
(4) Amines			
Aniline	34,034	−4055	(30)
p-Phenylenediamine ($NH_2C_6H_4NH_2$)	(31,400)	−6690	(23)
	(34,800)	−3290	(12)

$$\Lambda_j = c^j \left\{ \frac{1}{\omega - \omega_j} \left[\rho' - \frac{1}{2}S \int \phi_j H_X \phi_j \, d\tau \right] - S \right\} \tag{26}$$

In the integral $\int \varphi_j H_X \varphi_j d\tau$, the potential of the substituent is replaced by that of a neutral atom minus a missing π electron, and the former is neglected. Therefore, using the notation of Sklar and Lyddane (26), one has

$$\int \varphi_j H_X \varphi_j d\tau = -(c^j)^2(aa; bb) \tag{27}$$

Furthermore from equation 21′,

$$2\rho' = \int pH_R\zeta d\tau + \int pH_X\zeta d\tau = -Q_{12} - (Q_{12} + ab; bb) \tag{28}$$

Finally, since these integrals involve p functions belonging to different atomic numbers, Sklar's approximation (24) is introduced. The atomic integral will be designated so that *ab;bb* (C) means an integral *ab;bb* calculated for the atomic charge of C. Similarly S (C) will be the overlap calculated by the formula on p. 990 of reference 24, while S without index is calculated by formula 23 of reference 24.

TABLE 4

Data used in calculating red shift

	ω	ω_g	ω_e	$\frac{1}{2}[\ ]_g$ FROM EQUATION 29	$\frac{1}{2}[\ ]_e$ FROM EQUATION 29	S (C)	S (X)	S
F	15	9.9	7.8	28.5	26.1	0.273	0.058	0.131
OH...	12.5	9.7	7.6	20.6	18.2	0.283	0.100	0.201

TABLE 5

Calculated electron migration and red shift

	Λ_g	Λ_e	$(\omega - \omega_g)\Lambda^2_g$	$(\omega - \omega_e)\Lambda^2_e$	$\Delta\nu$ (CALCULATED)	$\Delta\nu$ (EXPERIMENTAL)
F	0.158	0.117	−0.128	−0.099	−230	−271
OH... .. .	0.362	0.184	−0.312	−0.167	−1170	−1739

Then

$$\Lambda_j = c^{(j)} \frac{S}{2} \left\{ \frac{1}{2} \frac{1}{|\omega - \omega_j|} \left[\frac{ab; bb\,(\mathrm{C}) + 2Q_{12}(\mathrm{C})}{S\,(\mathrm{C})} + \frac{ab; bb\,(\mathrm{X}) + 2Q_{12}(\mathrm{X})}{S\,(\mathrm{X})} \right.\right.$$
$$\left.\left. - (c^j)^2 S \left(\frac{aa; bb\,(\mathrm{C})}{S\,(\mathrm{C})} + \frac{aa; bb\,(\mathrm{X})}{S\,(\mathrm{X})} \right) \right] - 1 \right\} \tag{29}$$

The values of the atomic integrals at various distances were kindly supplied by Miss Virginia Griffing. The constants are (6, 25):

$$c_g^2 = \frac{1}{3.6}; \quad c_e^2 = \frac{1}{2.16}$$

The values of ω were taken from reference 24; the values of ω_g and ω_e were kindly supplied by Dr. A. L. Sklar.

Table 4 shows the data used and some of the values calculated for C_6H_5F

and C_6H_5OH. All energies are in electron volts. Table 5 shows the results of the calculations.

The agreement is much better than one could expect, particularly since the change in zero-point energies has been neglected. A decrease in the ionization potential of OH by 0.2 volt increases $|\Delta\nu|$ by 170.

From the data of table 4 an approximate formula seems to be:

$$\begin{aligned}\Lambda_g^2 &= \frac{S^2}{14.4}\left(\frac{27}{|\omega - \omega_g|} - 1\right)^2\\ \Lambda_e^2 &= \frac{S^2}{8.64}\left(\frac{19}{|\omega - \omega_e|} - 1\right)^2\end{aligned} \tag{30}$$

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APPENDIX I: MATHEMATICAL APPENDIX

Calculation of the coefficients

The mathematical argument in the general case of n particles is as follows: Consider the deflection of a particle expressed by the normal coördinates, i.e., the inverse equation compared to equation 6″:

$$x_1 = c_1^{(1)}X_1 + c_1^{(2)}X_2 \cdots + c_1^{(s)}X_s \cdots + c_1^{(n)}X_n$$

and for the s^{th} particle

$$x_s = \sum_j c_s^{(j)}X_j \tag{A1}$$

For a particular mode of vibration, e.g., the k^{th}, all X's but X_k are zero.

$$k^{\text{th}}\text{ mode: } x_1 = c_1^{(k)}X_k \qquad x_2 = c_2^{(k)}X_k \qquad x_s = c_s^{(k)}X_k \tag{A2}$$

If a geometrical discussion such as the one in the text shows that in the k^{th} mode

$$x_1:x_2:\cdots x_s:\cdots x_n = a_1^{(k)}:a_2^{(k)}:a_s^{(k)}:a_n^k \tag{A3}$$

then it follows that

$$c_1^{(k)} = a_1^{(k)}b_k \qquad c_2^{(k)} = a_2^{(k)}b_k \qquad c_s^{(k)} = a_s^{(k)}b_k \tag{A4}$$

where b_k is a common arbitrary factor. We decide, for reasons to be given below, to choose b_k so that

$$\sum_s (c_s^{(k)})^2 = 1, \text{ or } b_k^2[(a_1^{(k)})^2 + \cdots (a_s^{(k)})^2 + \cdots] = 1 \tag{A5}$$

Then and only then, the same coefficients can be used for the expressions which are the inverse ones to expression A1:

$$X_k = \sum_s c_s^{(k)}x_s \tag{A6}$$

In other words, it is permissible to read the following scheme either horizontally or vertically:

$$\begin{array}{c|ccc}
 & X_1 & X_2 & X_3 \cdots \\
\hline
x_1 & c_1^{(1)} & c_1^{(2)} & c_1^{(3)} \\
x_2 & c_2^{(1)} & c_2^{(2)} & c_2^{(3)} \\
x_3 & c_3^{(1)} & c_3^{(2)} & c_3^{(3)}
\end{array}$$

Mathematically, one says that the transformation matrix (c) is real orthogonal or, more generally, unitary.

APPENDIX II. OSCILLATION THEOREM

For a continuous string of arbitrary density distribution, one can prove (4) that every number of nodes is represented in one mode of vibration. For a membrane in a case where the variables can be separated, one has two sets of nodal lines, and one can prove that each combination of two numbers, giving the number of nodes in each set, is represented in one and only one mode of vibration.

I am not familiar with any strict mathematical proof that a similar theorem can be applied to the most general system of discrete particles, each tied only to its neighbor, although it seems very plausible. For an open chain of equal particles (and equal springs) or an open chain where all particles but the end particles are equal (3, 7, 8, 14), or for a closed chain of equal particles, or for a square of equal particles, the statement can be found correct by actually writing the solutions of the equations of motion, i.e., the modes of vibration. For regular arrangements as in crystal lattices, the statement can also be proved (1, 2).

APPENDIX III. THE ENERGY AS FUNCTION OF THE NUMBER OF NODES

In the case of a vibrating chord or membrane, it is easy to see that the frequency (and $4\,\pi^2\nu^2$) increases with an increase in the number of nodes (for a membrane, with an increase of the number of nodes of the same kind). If more nodes are inserted in a given length of string, the string is folded more closely and therefore the effective restoring force increases (mathematically $\left|\frac{d^2u}{dx^2}\right|$ increases).

Similarly, for a chain of discrete particles, one can see that the introduction of a new node brings a pair of neighboring particles, which before had been on the same side of the equilibrium position, to opposite sides, and therefore one or more springs are stretched to a greater degree than before, with a resulting increase of frequencies.

In the quantum theory, one can give a similar proof (1, 2). It shall be proved in particular that the electron energy in a molecule increases with the number of nodes in the molecular orbitals, for the case where repulsion between the electrons is included as well as when it is excluded.

We have to assume that there exists, between each pair of electrons as well as between each electron and the positive centers of the molecular skeleton, either a Coulomb potential A/r or no interaction.

Then one proves that the average total kinetic energy (including the motion of the nuclei in respect to the center of gravity) is equal to half the negative average of the potential energy, just as in classical mechanics (27):

$$2 \times \text{average kinetic energy} = -\text{average potential energy}$$

Therefore

$$\text{Total energy} = -\text{average kinetic energy} \tag{A7}$$

or

$$E = +\ \text{average}\ \Sigma \frac{h^2}{8\pi^2 m} \Delta = \int \Psi^* \left\{ \Sigma \frac{h}{8\pi^2 m} \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y} + \frac{\partial^2}{\partial z^2} \right) \right\} \Psi \, d\tau \tag{A8}$$

summed over all particles, where Ψ is the correct wave function belonging to the assumed potential-energy function. But the Δ operator measures again the absolute value of the curvature, and one sees therefore that the energy increases with an increase in the number of nodes of each kind.

The problem can be considered from a different standpoint. In the hydrogen molecular ion, one can write the energy of the two states originating from atomic 1*s* states (18):

$$E_g = E_0 + \frac{J + K}{1 + S} \quad \text{bonding} \tag{A9}$$

$$E_e = E_0 + \frac{J - K}{1 - S} \quad \text{antibonding} \tag{A9'}$$

J is the Coulomb integral and K the exchange integral, both negative. Upon subtraction, one finds

$$E_e - E_g = 2 \frac{JS - K}{1 - S^2} \tag{A10}$$

Therefore, E_e is higher than E_g only if $| K | > | J | S$. In the hydrogen molecular ion, this is the case; the preceding argument shows that it must always be the case if the correct eigenfunctions are chosen.

The same calculation can be made for a π π bond. This is a refinement of the treatment given in Section I,C for such bonds; it shows that in the bonding orbital the attractive effect of the negative charge between the two nuclei (K) is partly compensated by the fact that in the bonding orbital the electrons are less frequently near their nuclei than in free atoms or in the antibonding state (this is expressed by JS in the energy difference). For the correct wave function however, the bonding effect is always predominant.

On the other hand, one finds a difficulty in benzene. Excitation consists in lifting one electron from an orbital with one node (ψ_3 in Section I,D,(2)) to an orbital with two nodes (ψ_5). The molecular excited state turns out (6, 25) to lie higher than the unexcited one if the repulsion between electrons is taken into account. But the energy of orbital ψ_5, without electron repulsion, is lower than that of orbital ψ_3.

In terms such as given for the hydrogen molecular ion, the difference of the energy of the orbitals, which was just called $E_e - E_g$, is written as follows (6, 25):

$$\epsilon_2 - \epsilon_1 = \frac{\sigma_1 - \sigma_2}{\sigma_1 \sigma_2} \{ -2Q_s - 2\mathrm{A}_1 - 2\mathrm{A}_2 - \mathrm{A}_3 \} + \frac{\sigma_1 + \sigma_2}{\sigma_1 \sigma_2} (\mathrm{R} + \mathrm{B}) \tag{A11}$$

The σ are normalization factors. $\frac{\sigma_1 - \sigma_2}{\sigma_1 \sigma_2}$ corresponds to (and in case overlap between all but next nearest neighbors is neglected, is exactly equal to) $2 \frac{S}{1 - S^2}$; $\frac{\sigma_1 + \sigma_2}{\sigma_1 \sigma_2}$ corresponds to (and if overlap between all but next nearest neighbors is neglected, is exactly equal to) $\frac{2}{1 - S^2}$; $- 2Q - 2A_1 - 2A_2 - A_3$ corresponds to J and $R + B$ to $- K$. $\epsilon_2 - \epsilon_1$ turns out negative because $| J | S$ is larger than $| K |$, which should not be the case according to the general theorem if the correct eigenfunctions had been used. Therefore the fact that $\epsilon_2 - \epsilon_1$ turns out negative must be due to the choice of eigenfunctions, which are not correct for the potential chosen; in fact, the $2p$ functions used belong to a nuclear charge $3.18e$, while the skeleton potential was chosen with unit nuclear charge.

THE EFFECT OF ALKYL SUBSTITUTION ON THE SPECTRA AND IONIZATION POTENTIALS OF SOME FUNDAMENTAL CHROMOPHORES[1]

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The effect of alkyl substitution on the ionization potentials of electrons in chromophoric groups is illustrated by an extensive collection of best values. Thermochemical data are used to show that the reductions in ionization potential which accompany alkyl substitution are due to a relatively large stabilization of the molecular ion accompanying the introduction of the additional alkyl group. Although small stabilization of the unexcited neutral molecule occurs on alkyl substitution, this is of a lower order of magnitude than that associated with the ionic state. The greater relative stabilization of the molecular ion is implicit in the theory of hyperconjugation, but the effects observed seem to be larger than can be accounted for on the simple hyperconjugation theory. It is thought that various charge-transfer effects occurring in the ionic state are responsible for a great part of the reduction. The red shifts of many absorption bands on alkyl substitution are no doubt to be attributed, at least in part, to similar causes.

The wave length at which an absorption band occurs depends upon the difference between the energies of the ground and the excited states of the molecule absorbing the radiation. Any attempt to understand the wave-length shifts produced by different substituents in a chromophore must therefore take into consideration the effect of the substituent on the energies of both the upper and the lower states associated with the transition. For example, if the substitution of an alkyl group into benzene were found to increase the resonance energy of the ground state relative to that of benzene itself, it would still be necessary to know the change in the resonance energy of the excited state before the shift in the absorption band could be predicted. Conversely, the change in resonance energy or stability of the excited state can be predicted if the shift in the absorption band and the change in resonance energy of the normal state resulting from the substitution are known. In order to simplify matters somewhat it is convenient to consider first the ionization potentials of substituted molecules instead of their absorption spectra, since then it is only necessary to take into account the energies of the normal and the ionized states, and the difficulty of assessing the bonding or antibonding contribution of the excited electron is avoided. Table 1 contains a classified list of the ionization potentials of a large number of molecules which can be considered as derived from the first member of each class by alkyl substitution.

The values given in table 1 are in general believed to be accurate to within half

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TABLE 1

Table showing the effect of substitution on ionization potential

SUBSTANCE	IONIZATION POTENTIAL	REFERENCES
Hydrocarbons		
Hydrogen	15.427	(2, 32)
Methane	13.1	(33)*
Ethane	11.6	(8)*
Propane	11.3	(5)*
n-Butane and isobutane	10.34	(9)*
Hydrogen atom	13.595	(4)
Methyl radical	10.07	(10)*
Ethyl radical	8.67	(10)*
n-Propyl radical	7.80	(7)*
Isopropyl radical	7.77	(7)*
tert-Butyl radical	7.19	(7)*
Ethylene	10.50	(26)
Propylene	9.70	(9, 26)*
1-Butene	9.65	(35)*
2-Butene	9.24	(26)
Isobutene	8.95	(37)*
Trimethylethylene	8.80	(26)+
Tetramethylethylene	8.30	(26)+
Butadiene	9.07	(27)
β-Methylbutadiene	8.86	(27)
β,γ-Dimethylbutadiene	8.72	(27)
Benzene	9.24	(30)
Toluene	8.92	(29)
Ethylbenzene	*ca.* 8.75	Unpublished data +
Isopropylbenzene	*ca.* 8.6	Unpublished data +
tert-Butylbenzene	*ca.* 8.5	Unpublished data +
o-Xylene	*ca.* 8.3	Unpublished data +
m-Xylene	*ca.* 8.3	Unpublished data +
p-xylene	*ca.* 8.3	Unpublished data +
Naphthalene	8.3	(4)*
β-Methylnaphthalene	8.0	Unpublished data +
Acetylene	11.41	(21)
Methylacetylene	11.30	(28)
Alkyl derivatives of H_2O, H_2S, NH_3, HCHO, and the halogen acids		
Water	12.61	(23)
Methyl alcohol	10.8	(38)*
Ethyl alcohol	10.7	(38)*
Propyl alcohol	10.7	(38)*
Dimethyl ether	10.5	(38)*
Diethyl ether	10.2	(38)*
Hydrogen sulfide	10.47	(23)
Ethyl mercaptan	9.70	(38)*

TABLE 1—*Continued*

SUBSTANCE	IONIZATION POTENTIAL	REFERENCES
Dimethyl sulfide	9.40	(38)*
Diethyl sulfide	9.30	(38)*
Di-*n*-propyl sulfide	9.20	(38)*
Ammonia	10.8 (11.5)	(38)
Methylamine	9.8	(38)*
Dimethylamine	9.6	(38)*
Trimethylamine	9.4	(38)*
Formaldehyde	10.88	(22)
Acetaldehyde	10.23	(40)
Acetone	10.1	(18)
Hydrogen chloride	12.81	(25)+
Methyl chloride	11.25	(24)
Ethyl chloride	10.89	(24)+
n-Propyl chloride	10.7	(36)*
tert-Butyl chloride	10.2	(36)*
Hydrogen bromide	12.01	(25)+
Methyl bromide	11.17	(24)
Ethyl bromide	10.92	(24)
Hydrogen iodide	10.33	(25)
Methyl iodide	9.49	(24)
Ethyl iodide	9.34	(24)
Halogen-substituted hydrocarbons		
Ethylene	10.50	(26)
Vinyl chloride	10.00	(26)
cis-Dichloroethylene	9.66	(39)
trans-Dichloroethylene	9.96	(39)
Butadiene	9.07	(27)
Chloroprene	8.83	(27)
Benzene	9.24	(30)
Monochlorobenzene	8.8	(29)

a unit of the last figure given. In some cases, particularly that of the alkyl radicals, the error may be four or five times greater than this. The values determined from Rydberg series have been recalculated, using the conversion factor based upon the new value of the elementary charge. The electron-impact values have been given as quoted by the original author, as the increase of 0.5 per cent due to the new value of *e* is usually within the experimental error. Some ionization potentials have been estimated by considerations of spectroscopic features other than Rydberg series. These are marked +. In the case of unsaturated and aromatic hydrocarbons the electron removed is a π double-bond electron. For the other molecules the ionization is of a non-bonding electron, usually $p\pi$, localized on the nitrogen, oxygen, sulfur, or halogen atom, respectively. Electron-impact values are starred.

From the table it is clear that the substitution of a hydrogen atom by an alkyl group always has the effect of lowering the ionization potential. The amount of the lowering depends, among other things, upon the proximity of the alkyl group to the electron affected. What is considered to be most important in this connection, however, is the fact that the magnitudes of the changes, which are often of the order of 0.5 volt or 10 kcal. per mole, are far greater than any changes in ground-state stabilization (resonance energy) which have been shown by heats of hydrogenation or formation to accompany substitution. The conclusion to be drawn from this is that the main cause of the reduction is to be sought for in an increase in the stability of the molecular ion resulting from the substitution.

TABLE 2

Stabilization energy and reduction of ionization potential of alkylethylenes relative to ethylene (in kilocalories per mole)

SUBSTANCE	ΔC	ΔH	ΔI
Propylene	3.032	2.7	18.4
1-Butene	2.639	2.5	23.0
2-Butene (*cis*)	4.281	4.2	21.5
2-Butene (*trans*)	5.320	5.2	*ca.* 21.0
2-Methylpropene ("isobutene")	4.620	4.4	35.7
Trimethylethylene	5.970	5.8	39.2
Tetramethylethylene	6.140	6.2	49.5

MONOÖLEFIN HYDROCARBONS

The class of molecules for which the thermal data are most complete is the monoölefin hydrocarbons, and these will therefore be considered first. Table 2 gives the heats of stabilization relative to ethylene of the various alkylethylenes as obtained from heats of combustion (ΔC) (17) and hydrogenation (ΔH) (12), together with the diminutions in ionization potential of the π electrons, all quantities being expressed in kilocalories per mole. The ΔC's of table 2 were calculated in the following manner from heat of combustion data given in the A.P.I. tables (17):

$$\Delta C = \{C\ (\text{satd.}) - C\ (\text{unsatd.})\} - \{C\ (\text{ethane}) - C\ (\text{ethylene})\}$$

where C (satd.) is the heat of combustion of the corresponding saturated hydrocarbon. It is obvious that ΔC should be equal to ΔH from this equation, since H is equal to the heat of formation of 1 mole of water minus $\{C\ (\text{satd.}) - C\ (\text{unsatd.})\}$. The agreement between the two sets of values, which does not appear to have been previously pointed out, is very satisfactory. The fact that the C's are referred to a temperature of 25°C. and the heats of hydrogenation to 82°C. has negligible effects on this agreement, as can be shown by calculating the heats of combustion for the higher temperature from the extensive data of Rossini and collaborators (17).

The agreement between the ΔH's and ΔC's is incidental to the point being stressed here and is only given to show that the thermochemical values obtained for the stabilizations by alkyl substitution of the monoölefin hydrocarbons in their ground states are well founded. The important fact contained in table 1 is that the changes in ionization potential are much larger than the increases in stabilization of the normal states of the molecules. They are, in fact, in the opposite direction from what would be expected if the normal state alone and not the ionic state were affected by the substitution. The explanation must be that while both normal and ionized states are stabilized, the ionic state is stabilized to a relatively much greater extent. Thus, while the normal state of propylene has a stabilization energy of 3 kcal. per mole relative to ethylene, its ionic state is stabilized by as much as 21 relative to $C_2H_4^+$. Such stabilization of the ion is implicit in the molecular orbital description of the hyperconjugation

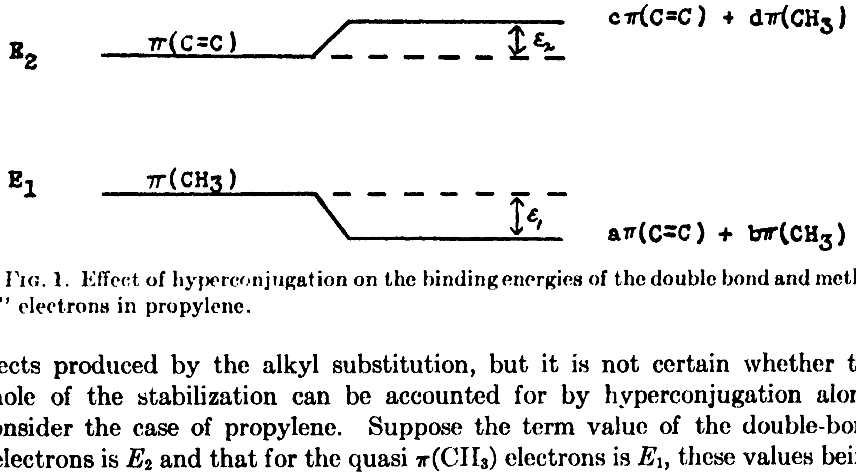


FIG. 1. Effect of hyperconjugation on the binding energies of the double bond and methyl "π" electrons in propylene.

effects produced by the alkyl substitution, but it is not certain whether the whole of the stabilization can be accounted for by hyperconjugation alone. Consider the case of propylene. Suppose the term value of the double-bond π electrons is E_2 and that for the quasi $\pi(CH_3)$ electrons is E_1, these values being roughly equal to the ionization potential of the unbound electron plus its contribution to the energy of the bond (β_2, β_1). Then the interaction of these π orbitals will lead to a lowering of E_2 by ϵ_2 and a raising of E_1 by ϵ_1. Thus, the stabilization energy of propylene relative to ethylene arising out of hyperconjugation is $2(\epsilon_1 - \epsilon_2)$, while the first ionization potential has dropped by an amount ϵ_2 and the ion is stabilized by an amount $(\epsilon_1 - \epsilon_2) + \epsilon_1$. For propylene $2(\epsilon_1 - \epsilon_2) = 3$ kcal. and $\epsilon_2 = 18.4$ kcal., hence $\epsilon_1 = 19.9$ kcal. Now, the magnitudes of ϵ_1 and ϵ_2 would not be expected to be more than 10–20 per cent of the values β_1 and β_2, as the changes arising from full conjugation as in butadiene are only about 40 per cent β. On this hypothesis the magnitudes of β_1 and β_2 would be expected to be roughly 100–150 kcal. The old value for β_2 used to be about 18 kcal., later being stepped up to 35 kcal. (13). However, Professor R. S. Mulliken thinks that it might be raised to as much as 70 kcal. Unless this high value for β_2 is substantiated, it appears that some additional effect will have to be postulated to explain the large reductions in ionization potential in going from ethylene to propylene. It should be mentioned, however, that the red shifts of the alkylethylenes in their 1800 A. bands appear to be completely accounted for in terms of hyperconjugation (16). The author believes that an additional effect which brings about stabilization of the molecular ion may be in the nature of a charge transfer which comes into operation on the excitation or ionization of an electron. It is assumed that any charge transfer which occurs in the normal, excited, or ionized state brings about stabilization by resonance to ionic structures. In the case of the normal state of propylene charge can only migrate into the double bond by making use of the $(x - x)$ or higher occupied orbitals. However, in the ion charge can flow into the low $x + x$ orbital which has been vacated. Much more charge can flow in this case than in that of the neutral molecule and much greater stabilization can thereby be produced. While the polar state of the normal molecule, *viz.*,

$$H_3^+ \doteq C\cdot - CH^- \cdot CH_2$$

is an improbable one, the polar state of the ion, $H_3^+ \doteq C—CH{=}CH_2$, is much more likely and probably makes a considerable contribution to the stability of the $H_3{\equiv}C\ \ CH^+ \doteq CH_2$ ion. The fact that the more highly excited shorter-wave-length absorption bands suffer larger shifts on substitution than do the longer-wave-length bands of a molecule also fits in with the above explanation, since it is to be expected that the more completely an electron is removed the greater will be the ensuing charge migration.

The above idea can be expressed in terms of molecular orbital theory in the following way: Firstly, it should be stated that a certain amount of charge transfer for the ion is contained in the idea of hyperconjugation. If there were no hyperconjugation, then on ionization the double bond would lose one electron. However, as a result of the hyperconjugation it only loses a fraction of an electron, the amount depending on the coefficients a and b in the mixed orbital $a\phi(\pi, C{=}C) + b\phi(\pi, CH_3)$. The corresponding orbital for the quasi πCH_3 electrons can be written $c\phi(\pi, C{=}C) + d\phi(\pi, CH_3)$, where $d \gg c$ in the ground state. It is thought that in the ionized state c will increase considerably as a result of the increase in electron affinity of the ethylenic bond on ionization and this will result in the sort of charge transfer described above. Such an additional charge transfer would not be expected where there is complete conjugation as in butadiene, as both double bonds would be equally affected and there would be no change in the mixing coefficients.

ALKYLBENZENES

Another set of molecules for which thermochemical data are available on the effect of substitution of the normal states is that of the alkylbenzenes (17). The heats of hydrogenation diminish with substitution as in the alkylethylenes, but the stabilization produced is not quite so great as in the former class of molecules, possibly because of the resonance stabilization already present. However, judged from a criterion given in a later section, *viz.*, that stabilization energy = 157.4 − {C (RX) − C (HX)}, which takes some account of paraffinoid as well as resonance stabilization, the effect in aromatics (*ca.* 2.9 kcal.) is much more comparable with that in olefins (*ca.* 2.65 kcal.), both being about half the value found for the acetylenes (4.8 kcal.). The available hydrogenation data obtained in a manner similar to that used for table 2 are given in table 3.

It will be noted that both ΔH and ΔI are smaller than for the alkylethylenes. As explained in connection with the alkylethylenes, the effect of the hyperconjugation is to lower the ionization potentials of the aromatic π electrons and to increase that of the quasi πCH_3 electrons, yielding a resultant stabilizing energy of the ground state and a much greater stabilization of the molecular ion. The explanation of the relatively greater stabilization of the molecular ion follows essentially the same lines as that already given for the ethylene derivatives. Firstly, a large proportion of it is explicable in terms of ordinary ideas of hyperconjugation. Secondly, there may be a further charge-transfer effect arising out of the migration of methyl electrons into the low orbital of the ring which has been vacated by the electron which has been ionized. This latter effect may be the same thing as saying that the molecular orbitals in the ion differ from those in the neutral molecule by having the mixing coefficient of the aromatic π orbital increased relative to that of the alkyl π orbital as a result of the increased electronegativity produced in the ring by the ionization. In the normal molecule resonance between the aromatic and alkyl π electrons is limited by the fact that their energies are considerably different, their ionization potentials being *ca.* 9 and 12 volts, respectively. In the ion, which has lost an aromatic π electron, the ionization potential may be much more evened out by the relatively greater increase of the ionization potential of the ring electrons compared to those of the substituent and both may now require, for instance, *ca.* 20 volts for their removal. This increased resonance leads to increased stabilization of the ion and implies considerable charge transfer from the methyl radical to the ring.

TABLE 3

Stabilization energy and reduction of ionization potential of alkyl aromatics relative to benzene (in kilocalories per mole)

SUBSTANCE	ΔC	ΔH	ΔI
Toluene	0.30		9.7
Ethylbenzene	1.16	0.9	*ca.* 11.3
n-Propylbenzene	1.17		*ca.* 14.7
n-Butylbenzene	1.59		
n-Pentylbenzene	1.59		
n-Hexylbenzene	1.59		
o-Xylene		2.5	*ca.* 18.0
Mesitylene		2.2	*ca.* 25.0

The differences of ionization potential in the pairs ethylene–propylene, benzene–toluene, and acetylene–methylacetylene are 0.80, 0.42, and 0.11 volt, respectively. The low value of the difference between acetylene and methylacetylene means that the methylacetylene ion is not preferentially stabilized to any great extent by the resonance charge-transfer effects referred to above. This is understandable qualitatively, as it is known that such charge transfer occurs to a considerable extent in the ground state of the molecule and the amount of additional charge transfer that can take place in the ion is therefore somewhat limited.

All *NV* bands of the alkylbenzenes are stronger than they are in benzene itself, indicating hyperconjugation (16). This involves a charge transfer, the effect of which may be enhanced by an alteration of the mixing coefficients for the aromatic and alkyl π orbitals in the excited state as suggested for the ions. The f values found for the xylenes (20) are greater than unity, presumably because some of the intensity is drawn from the alkyl π electrons. Only the Rydberg bands appear to lose intensity, and this may be because they are blurred out by predissociation or other effects.

It should be pointed out that extensive resonance can often occur without it being apparent from thermochemical data. For example, the heat of hydrogenation of styrene is very little different from that calculated for the isolated aromatic and ethylenic double bonds. However, it is obvious from the spectra that there is intimate mixing between the aromatic and ethylenic orbitals which are very considerably affected by the resonance. The resonance energy in the ground state is a net effect which might well change only slightly, though the contributing factors alter appreciably.

SATURATED PARAFFINS

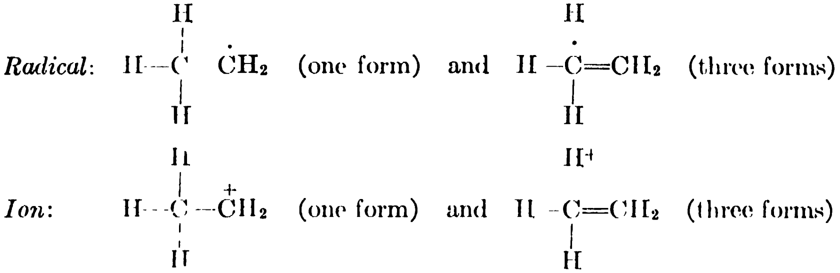
The next set of molecules to be considered are the saturated hydrocarbons. It is not possible to assign energy values to one class of electrons in this case in the same way that heats of hydrogenation can be associated with double-bond electrons in olefins and aromatics. However, in a crude approximation we only have to deal with electrons in single C—H and C—C bonds. This is not strictly the case, as is brought out by Mulliken's molecular orbital treatment (14). To a first approximation the ionization potential and absorption spectra of methane can be attributed to electrons in C—H bonds. For ethane and higher hydrocarbons, the lowest ionization potentials are taken to be those of electrons in C—C bonds. It is seen from table 1 that lowering of the ionization potential occurs with increased number of C—C bonds. This is probably to be related to the fact that an increasing number of bond structures can be written for the molecular ion with increase in the number of carbon atoms it contains. Thus $C_2H_6^+$ has one structure, $C_3H_8^+$ has two, $C_4H_{10}^+$ has three, and so on. The more highly branched a substance is the more of these structures become equivalent, causing further stabilization which may be reflected in the ionization potential. Taking into account charge transfer, two more structures of the type

$$H_3^+ \overset{\cdot}{=} C - C \equiv H_3$$

must be considered for $C_2H_6^+$, three for $C_3H_8^+$, four for $C_4H_{10}^+$, etc., and no doubt these contribute appreciably to the stability of the ion. Stabilization by branching appears to be somewhat offset by comparable stabilization occurring in the ground state. Thus the electron-impact experiments of Hipple and Stevenson (9) were unable to detect appreciable differences between the ionization potentials of *n*-butane and isobutane.

ALKYL RADICALS

The possible variation in the ionization potentials of different radicals arising from different amounts of resonance energy in the normal and ionized states was considered by Baughan, Evans, and Polanyi (1). They wrote the following structures as possible resonance forms of the ethyl radical and its ion



Radical: $H{-}\overset{H}{\underset{H}{C}}\ \dot{C}H_2$ (one form) and $H{-}\overset{\overset{H}{\cdot}}{\underset{H}{C}}{=}CH_2$ (three forms)

Ion: $H{-}\overset{H}{\underset{H}{C}}{-}\overset{+}{C}H_2$ (one form) and $H{-}\overset{H^+}{\underset{H}{C}}{=}CH_2$ (three forms)

and concluded on the basis of these structures that the resonance in the radical and in the ion are comparable and that there should not be much difference in the ionization potentials of the methyl, ethyl, isopropyl, or *tert*-butyl radicals. The resonance in the ethyl radical was computed to be only about 7 kcal.; that of the isopropyl and tertiary butyl radicals (resonance among seven and ten forms, respectively) was computed to be somewhat greater, but the authors concluded that the ionization potentials of the various radicals did not differ greatly because in all cases the resonance energy of the ion did not appear to be very different from that of the normal state of the molecule. It was subsequently shown by experiment (7, 10) that there is a great deal of variation amongst these ionization potentials. The explanation of this appears to be fairly clear in terms of the concepts already outlined and is as follows: There is much greater stabilization of the ethyl ion by virtue of the hyperconjugation of the quasi π orbitals of the methyl group with the vacated π orbital of the methylene group.

$$H_3{\equiv}C{-}\overset{+}{C}{=}H_2 \qquad H_3^{+}{\cdot}{-}C{-}\dot{C}{=}H_2$$

This incidentally results in considerable charge transfer from the methyl group into the methylene group by hyperconjugation, an effect which does not occur to nearly the same extent in the neutral radical. Thus, the ion is stabilized considerably relative to the neutral ethyl radical and this reduces its ionization potential compared to that of the methyl radical, whose ion is not stabilized by the same process. On the molecular orbital theory the ethyl radical is somewhat similar to the three-center problem discussed by Hückel (11), who considers the allene radical. It differs in so far as the quasi π and ethylenic $p\pi$ orbitals are not equivalent. Hückel's simple treatment leads to one strongly bonding, one non-bonding, and one antibonding molecular orbital. In the ethyl radical these may be thought of as the bonding π (CH_3) orbital depressed by resonance with the ethylenic $p\pi$, the antibonding orbital elevated (or made more antibonding) from the same cause, and the non-bonding ethylenic orbital remaining unchanged as a result of mutually opposing effects from the two orbitals already mentioned. In practice, it appears that the depressing effect of the antibonding orbital is considerably less than the elevating effect of the bonding orbital, so that the non-bonding orbital becomes appreciably antibonding. In the neutral radical two electrons would occupy the first orbital and one would have to go into the slightly antibonding orbital. This last electron would be the one corresponding to the first ionization of the radical. The radical ion is stabilized because the remaining electrons are in fully bonding orbitals. Further, as a result of the ionization, which is mainly located in the CH_2 group, there will be an adjustment in the mixing coefficients of the bond orbitals and additional charge transfer and stabilization are to be expected from this effect.

Another explanation of the low ionization potentials of the radicals which has to be considered is connected with the possibility that the radicals might be bent in their normal states (like ammonia and the amines) and might acquire a more stable planar configuration on ionization, the repulsion between methyl groups bound to a tetrahedral carbon being less when they are in a planar configuration bound to a trigonal C^+. However, it appears that the energies of the in-plane and out-of-plane configurations only differ by a small fraction of a volt (as can easily be shown to be true in the case of ammonia). Also, the packing of many methyl groups on to a carbon atom actually has a stabilizing and not a destabilizing influence, as indicated by the fact that the heats of combustion of branched-chain hydrocarbons are always a few kilocalories less than those of straight-chain hydrocarbons. Finally, the ionization potentials of the radicals run very closely parallel to, and roughly 3 volts less than, those of the corresponding hydrocarbons where there is little probability of change in geometrical shape on ionization. As a result, it is felt that such a change cannot have a major effect upon the ionization potentials of the radicals and the changes which do occur are not fundamentally very different from those which give rise to the reductions in ionization potential of the saturated hydrocarbons.

Rough values for the relative stabilization of the normal and ionized states of the radicals can be obtained from the data on the alkyl iodide bond strengths quoted by Evans (7) The energy required to dissociate the alkyl iodide into radical and iodine atom is given as 54 kcal. per mole for methyl iodide, 52 for ethyl iodide, 50 for *n*-propyl iodide, 46.5 for isopropyl iodide, 49 for *n*-butyl iodide, and 45 for *tert*-butyl iodide. Assuming this variation to be mainly due to the stabilization of the radical and using the values of the ionization potential of the radical given in the table, we get the values in table 4 for the stabilization energies in the radical and its ion relative to the methyl radical.

As with paraffins, increasing the number of carbon atoms leads to an increase in the number of resonance structures, and increased branching leads to more of these structures becoming equivalent. The stabilization due to branching oes not seem to be greatly different for the molecule and its ion. The effects of the varying ionization potentials of the radicals on the unimolecular reactions of the alkyl halides have been discussed by Evans (7).

ALKYL DERIVATIVES OF H_2O, H_2S, NH_3, HCHO, AND THE HALOGEN ACIDS

Table 1 shows that the substitution of alkyl groups for hydrogen atoms produces large reductions in the ionization potentials in the classes of molecules which can be considered as the alkyl derivatives of water, hydrogen sulfide, ammonia, formaldehyde, and the halogen acids. The electrons concerned in these cases are the non-bonding electrons on the appropriate atoms (except for a minor difference in the case of nitrogen). It is clear that the amount of lowering of the ionization potential of RX relative to HX is greatly influenced by the electronegativity of the group X (R being the alkyl substituent). The contribution of hyperconjugation to the lowering of the ionization potential can probably be explained along the lines already indicated for propylene and the ethyl radical. It is necessary to consider the hyperconjugation between an alkyl group and an atom or group X with which are associated two or more π orbitals (usually non-bonding atomic orbitals) and to take some account of the effect of the electronegativities of X on the mixing coefficients in the molecular orbitals. With the exception of the alkyl derivatives of formaldehyde, the problems reduce to the three-center problem similar to that discussed for the ethyl radical. The centers are of course not equivalent, as they are for the allene radical discussed by Hückel. As a simplification we shall discuss the resonance interaction of the bonding and antibonding molecular orbitals of the alkyl group with the non-bonding X orbitals. The relative magnitudes of the interactions between these orbitals will depend on how close the energies (term values) of the non-bonding orbitals are to those of the bonding orbitals. In most cases they lie closer to the bonding than to the antibonding orbitals but at somewhat lower energies (i.e., less tightly bound) than the bonding orbitals themselves, so that the interaction elevates them to a greater extent than the interaction with the antibonding orbitals depresses them. This leads to a reduction in ionization potential for the non-bonding X electrons with an increase in the stabilization energy of the ion RX^+. Both these effects can be enhanced by a changing of the mixing coefficients as a result of the removal of the X electron and in this way lead to still further decrease in ionization potential.

TABLE 4

Stabilization of alkyl relative to methyl radical (ion) (in kilocalories per mole)

	ETHYL	*n*-PROPYL	ISOPROPYL	*n*-BUTYL	*tert*-BUTYL
Radical	2	4	7.5	5	9
Ion	34	56	60.5		76

Although it is only necessary to consider the relative changes of stabilization energy between RX and RX^+ to explain the reductions in ionization potential, it is important to have some idea of the *absolute* changes in the stabilization energy of the molecules as a result of alkyl substitution in order to appreciate the nature of the effects taking place. It is not so simple to find data which will indicate the stabilization of the molecule as a whole in passing from HX to CH_3X comparable, for example, to the way in which the heats of hydrogenation of ethylene and propylene indicate the stability of the latter with respect to the former. However, another method is available which will give some idea of the magnitude of this effect. Table 5 gives the heats of combustion at 25°C. of various classes of molecules in the gaseous state to give gaseous carbon dioxide and liquid water. If one takes the difference between the heats of combustion of two successive members of a straight-chain homologous series, then provided this is done for sufficiently high members, the value obtained will be 157.4 kcal. per mole. This can be taken as the contribution to the heat of combustion of a molecule by replacement of a hydrogen atom by a methyl group if there is little interaction of the methyl group with the rest of the molecule, i.e., no change in the resonance energy of the molecule. The difference between 157.4 and any increment observed can be taken as the stabilization energy resulting from the substitution, i.e.,

$$\text{Stabilization energy} = S = 157.4 - \{C\ (\text{RX}) - C\ (\text{HX})\}\ \text{kcal. per mole}$$

$\Delta_1 C$ is the increment when a primary hydrogen atom not forming part of a methyl group is replaced; $\Delta_2 C$ is the increment for replacing the hydrogen atom of a methyl group. Most of the values are taken from Wheland (41) and come originally from a table compiled by M. S. Kharasch and W. G. Brown; the remainder were obtained from Bichowsky and Rossini (3). S^+ is the change in stabilization energy of the ion as a result of substitution and is obtained by simply adding to S the change in ionization potential.

Let us consider first the alkyl derivatives of water. The introduction of the first methyl group produces destabilization. Presumably, the break-up of the fairly compact electronic structure which is possible in H_2O is responsible for this. Any stabilization by hyperconjugation between the methyl group and the non-bonding electrons of the oxygen atom is inadequate to counteract it. An effect which accompanies this and may be significant in its explanation is a reduction of the polarity of the bond to the oxygen—the moment of the carbon-oxygen bond is only 0.8 D as compared with 1.51 D for the oxygen-hydrogen bond. It is presumably possible for the oxygen to take an electron from a hydrogen atom and form a "neon-like" electronic structure more easily than it can do so with an electron in an orbital attached to an alkyl group. Following the initial destabilization there is a subsequent small increase in stability in going from methyl to ethyl and a still smaller one in going from ethyl to *n*-propyl. This is presumably associated with stabilization arising out of the increased polarizability of the alkyl group. In going from methyl alcohol to dimethyl ether, i.e., another primary replacement, there is destabilization, but it is not so great as that associated with the first replacement of hydrogen. Similar changes are observed to a lesser degree in the amines, and the same remarks about the moments of the nitrogen-hydrogen and nitrogen-carbon bonds can be made as for

TABLE 5

Heats of combustion, CH_2 increments, and derived stabilization energies of various classes of molecules (in kilocalories per mole)

SUBSTANCE	C	Δ_1C	Δ_2C	S	S^+
Water	10.5				
Methyl alcohol	182.6	172.1		−14.7	27.0
Ethyl alcohol	336.8		154.2	3.2	
n-Propyl alcohol	493.3		156.5	0.9	
Dimethyl ether	346.7	165.0		−7.6	− 0.7
Diethyl ether	660.3		156.3	1.1	
Ammonia	90.8				
Methylamine	256.9	166.1		−8.7	14.3
Ethylamine	413.1		156.2	1.2	
Dimethylamine	418.2	161.3		−3.9	0.7
Diethylamine	730.6		156.2	1.2	
Trimethylamine	579.5	161.3		−3.9	0.7
Triethylamine	*ca.* 1042.0		154.1		
Hydrogen sulfide	134.0				
Methyl mercaptan	297.6	163.6		−6.2	*ca.* 11.0
Ethyl mercaptan	452.0		154.4	3.0	
Dimethyl sulfide	455.6	158.0		−0.6	6.3
Hydrogen cyanide	159.0				
Methyl cyanide	310.4	151.4		6.0	*ca.* 29.0
Ethyl cyanide	461.6		154.2		
Acetylene	310.615				
Methylacetylene	463.109	152.594		4.8	**−2.5**
Ethylacetylene	620.86		157.75	−0.35	
1-Pentyne	788.08		157.17	0.23	
Dimethylacetylene	616.533	153.424		4.0	
2-Pentyne	774.33		157.8		
Ethylene	337.234				
Propylene	491.987	154.753		2.7	**21.1**
1-Butene	649.757		157.77	−0.37	**0.6**
1-Pentene	806.85		157.09	0.31	
trans-2-Butene	647.072	155.85		1.5	
trans-2-Pentene	804.26		157.19	0.21	
trans-2-Hexene	961.66		157.40	0.0	
Benzene	789.08				
Toluene	943.58	154.50		2.1	11.8
Ethylbenzene	1101.13		157.55	−0.15	
n-Propylbenzene	1258.24		157.11	0.29	
Hydrogen	68.3				
Methane	212.80	144.0		+13.0	66.0
Ethane	372.82	(160.0)	160.0	−2.5	32.0

TABLE 5—*Continued*

SUBSTANCE	C	Δ_1C	Δ_2C	S	S^+
Propane	530.605		157.785	−0.045	6.9
n-Butane	687.982		157.377	+0.023	
Formaldehyde	131.7				
Acetaldehyde	281.7	150.0		7.4	22.4
Acetone	431.6	149.9		7.5	10.5
Diethyl ketone	746.8		156.1		
Hydrogen chloride	12.1				
Methyl chloride	164.2	152.1		5.3	41.9
Ethyl chloride	316.7		152.5	4.9	13.2
Hydrogen bromide	25.54				
Methyl bromide	184.0	158.5		−1.1	18.9
Ethyl bromide	340.5		156.6	0.9	6.6
Hydrogen iodide	160.4				
Methyl iodide	200.5	160.4		−4.0	15.3
Ethyl iodide	357.8		157.3	0.1	3.4

those of the oxygen-hydrogen and oxygen-carbon bonds. The molecular ions in practically all cases are stabilized by substitution, the amount of stabilization being greater the greater the electronegativity of the central atom and considerably exceeding in magnitude the stabilizing or destabilizing effects which occur in the ground state.

When a methyl group replaces a hydrogen atom in acetylene, ethylene, benzene, hydrogen cyanide, or formaldehyde, stabilization occurs. This is largest when polar groups are involved, that is, in hydrogen cyanide and formaldehyde, indicating stability from charge transfer for these molecules in addition to simple hyperconjugation effects. The stabilization in methylacetylene is roughly twice that in propylene and toluene, in agreement with the two-dimensional character of the hyperconjugation for this molecule.

If one takes molecular hydrogen as the first member of the paraffins, then considerable stability is acquired in passing to the symmetrical molecule methane, an effect which is even more pronounced for the ion. This is, no doubt, to be associated with the great symmetry of the electronic structure of methane. In going to ethane this symmetry is lost, and the hyperconjugation stability which sets in is not adequate to offset the resulting destabilization.

The methyl derivative of hydrogen chloride has definite stabilization energy with respect to its parent, a fact which is contrary to what one might expect from analogy with the oxygen derivatives. Unfortunately, thermochemical data on the fluorine compounds is not available, but it is thought that for these compounds the analogy might be closer with oxygen derivatives, as there are possibilities of charge-transfer effects in heavier atoms which are not open to first-row atoms (i.e., possible use of $3d$ orbitals). Stabilization by two-dimensional hyperconjugation is of course possible for the alkyl halides. The molecular ions are stabilized greatly by methyl substitution, no doubt as a result of processes which lead to very considerable charge migration in the ion, which thus resonates between the forms R—X^+ and R^+—X. The lower the ionization potential of R, the greater this resonance would be expected to become, a conclusion which fits in with the lower ionization potentials for the isopropyl chlorides, *tert*-butyl chlorides, etc.

ABSORPTION SPECTRA

The long-wave-length shifts of absorption bands in general parallel the reductions in ionization potentials on alkyl substitution, though the wave-length shifts are of smaller magnitude because the excited state is not so strongly stabilized as the ionic state by hyperconjugation and charge transfer. Other effects are also present which sometimes give rise to small short-wave-length shifts. However, it is felt that only by considering separately the energy changes in the ground and in the excited states, as has been done here for the ionization potentials, will it be possible to get at the causes for some of the anomalous shifts observed. It is hoped that this principle will be carried over in a future paper dealing more specifically with absorption spectra, in particular the spectra of the substituted aromatics.

SUMMARY

The effect of alkyl substitution on the absorption spectra and ionization potentials of many classes of molecules is shown to be due mainly to preferential stabilization of the ionic or excited state. It is suggested that this is largely a result of hyperconjugation and charge transfer. Thermochemical and other data are used to support the arguments.

In conclusion, the author wishes to thank Professor R. S. Mulliken for many stimulating discussions on the broader aspects of the problems treated. His thanks are also due to the U. S. Office of Naval Research for sponsoring this project.

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THE NEAR-ULTRAVIOLET ABSORPTION SPECTRA OF MONOALKYL-SUBSTITUTED BENZENES[1]

Hyperconjugation and the Baker–Nathan Effect

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The near-ultraviolet absorption spectra in the vapor of toluene, ethylbenzene, the *n*- and iso-propylbenzenes, and the *n*-, *sec*-, and *tert*-butylbenzenes have been obtained. It is found that the 0–0 shifts, the intensity, and the internal distribution of intensity are of such a nature as to indicate that the methyl group hyperconjugates to the greatest extent and the *tert*-butyl group to the least extent with the ring. This is the spectroscopic analogue of the Baker Nathan effect, that the methyl group is a stronger directing group for ortho–para substitution in the ring than is the *tert*-butyl group.

INTRODUCTION

Substituted benzenes have spectra in the near-ultraviolet region which are closer to the visible and are more intense than is the spectrum of benzene. In general, greater wave-length shift and greater intensification are observed for those substituents which have large directing power toward a subsequent electrophilic substituent. The directing substituents have mobile electrons which can resonate with or migrate into the ring, such as substituents having unshared pairs of electrons on the alpha atom, —F, —Cl, —OH, —NH$_2$[2] and unsaturated groups which are conjugate to the ring, such as $-CH{=}CH_2$. An inductive effect related to the electron affinity of the substituent also operates, either in the same direction or opposite to the resonance effect.

A. L. Sklar (16) has discussed in detail the effect of migration of electrons from substituent to the ring on the intensity of the spectra. He shows that the intensity is a function of the extent of migration, which in turn depends on the presence of non-bonded electrons in suitably oriented p orbitals as well as on the electron affinity of the substituent.

K. F. Herzfeld (8) has obtained similar expressions for the term values of the ground and excited states as a function of the extent of migration. His formulae indicate that for these compounds the wave-length shift parallels the intensification.

Alkyl substituents, while not possessing formal unshared pairs of electrons or a structure which is conjugate to the ring, can nevertheless resonate with the ring in what has been called "hyperconjugation" by Mulliken, Rieke, and Brown (13). Here the single bonds on the α-carbon atom may act as electron donors to the ring. The methyl group has approximately the same effect on intensity, wave-length shift (15), and directing power as has the chlorine atom. Sklar (16) has calculated the intensity of absorption in the near-ultraviolet region for toluene and has obtained excellent agreement with experiment.

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[1] Presented at the Symposium on Color and the Electronic Structure of Complex Molecules which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago, Illinois, December 30 and 31, 1946.

[2] For the spectra of C_6H_5F, C_6H_5Cl, C_6H_5OH, and $C_6H_5NH_2$ see references 6, 10, 16, and 21.

Little has been published on the effect of the structure of alkyl groups on the spectrum. The treatment of hyperconjugation mentioned above deals with the ground state and the over-all effect of alkyl groups on acceptor bonds. It does not emphasize differences between alkyl groups except to state ". . . the computed contribution to the total π conjugation energy per bond is practically the same for CH_3 linked to $C{=}C$ as for $-CH_2-$. . . ."

TABLE 1

Dipole moments

R	RCl (20)	RC_6H_5 (2)
	D	*D*
Methyl	1.87	0.37
Ethyl	2.05	0.58
n-Propyl	2.10	
Isopropyl	2.15	0.65
n-Butyl	2.09	
sec-Butyl	2.12	
tert-Butyl	2.13	0.70

The difference in structure of the alkyl groups should be more apparent for the excited state (8). The electronic excitation in mononuclear aromatic spectra is of the form

$$x_1^2x_2^2x_3^2 \rightarrow \begin{cases} x_1^2x_2^2x_3x_4 \\ x_1^2x_2^2x_3x_5 \\ x_1^2x_2x_3^2x_4 \\ x_1^2x_2x_3^2x_5 \end{cases}$$

where the x's represent molecular orbitals for the π electrons of the ring. The energy of these orbitals is in the following order:

$$E(x_1) < E(x_2) = E(x_3) < E(x_4) = E(x_5) \qquad (7,\ 12)$$

Thus the excited state, having a vacant low-lying orbital, is a more enthusiastic electron acceptor than the ground state. (Qualitatively this accounts for the fact that the excited state is lower lying when electrons migrate into the ring.) Phenomena involving the excited state should be much more affected by differences in the electron-donating power of the substituent.

ELECTRON AFFINITIES AND POLARIZABILITIES OF ALKYL GROUPS

The dipole moments given in table 1 seem to indicate differences in the polarizabilities and perhaps the electron affinities of the various alkyl groups.[3] Sklar (16) has estimated the electron affinity of the methyl group to be 1.8 e.v. Applying the same method of calculation to other alkyl groups, the values given in table 2 were found.[4] The significance of these calculations is obscure, since it assumes that the excess positive and negative charges are localized on either end of the halogen-carbon bond. Furthermore, zero dipole moments have been reported for all paraffins. However, these data do seem to indicate that the ease of electron withdrawal is in the order $CH_3 < C_2H_5 < i\text{-}C_3H_7 < t\text{-}C_4H_9$. One might expect then that, other factors being constant, the intensity and the wave-length shift of the spectra will follow the same order. That this is not the case will be seen from the data presented below.

TABLE 2

Estimated electron affinities

ALKYL GROUP	ELECTRON AFFINITIES
	e.v.
Methyl	1.8
Ethyl	1.4
n-Propyl	1.0
Isopropyl	~1.0

EXPERIMENTAL DATA

In figure 1 are plotted the wave lengths of the 0-0 bands from the spectra of various alkyl-substituted benzenes, both in the vapor state and in solution. The vapor data are from Robertson, Chuoke, and Matsen (14) and the solution data from the reports of the American Petroleum Institute, Project 44 (1). The 0-0 band in benzene is forbidden, but its position in the vapor state has been calculated by Sponer, Nordheim, Sklar, and Teller (17) to be 2625 A. We have estimated the 0-0 band in solution to be 2640 A. from a comparison of the solution and vapor data for the substituted benzenes. It will be seen that the largest shift is for toluene and that *tert*-butylbenzene is shifted least from the position occupied by benzene.

The word "intensity" is generally taken to mean the integrated intensity for the entire electronic transition. However, equally interesting information can be obtained from the intensities of the individual bands. In figure 2 are plotted the molar extinction coefficients for the 0–0 bands. As was mentioned above, the 0–0 band in benzene is missing; consequently its extinction coefficient is zero. These extinction coefficients are calculated from the reports of the American Petroleum Institute Project 44 (1). Work on absolute intensities in the vapor phase has begun in this Laboratory; up to this time there has been established only the trend in the curve after toluene. It will be seen that the extinction coefficients of the 0–0 bands show the same sort of dependence on the substituent as was observed for the wave lengths of these bands.

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[3] The authors wish to acknowledge a conversation with Professor G. W. Wheland on this point.

[4] It was not possible to carry out the calculations for higher members of the series because the pertinent dipole-moment data were lacking. In the course of these calculations the electron affinities of $-NO_2$ and $-CN$ were estimated in an attempt to acquire more data to aid in the determination of the slopes of the charge *versus* electron affinity lines for the higher alkyl groups. These were found to be 6.5 for $-NO_2$ and 7.0 for $-CN$.

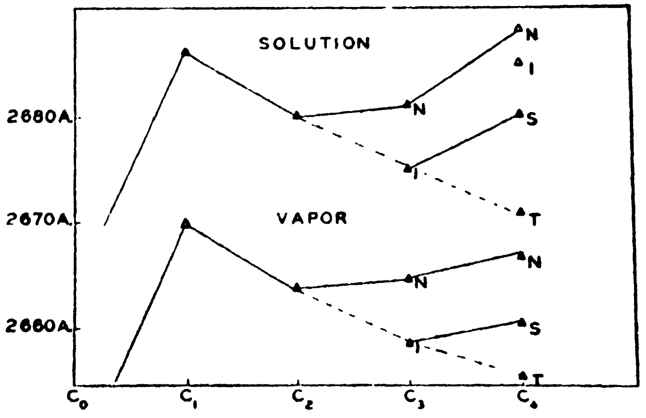

FIG. 1. Wave lengths of the 0–0 bonds in monoalkyl-substituted benzenes

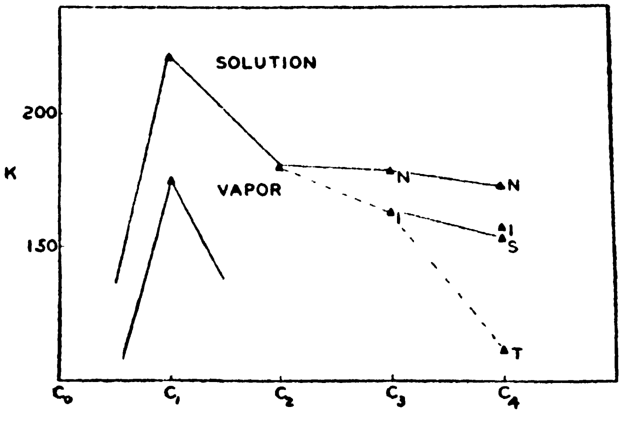

FIG. 2. Extinction coefficient (moles per liter) of the 0–0 bonds of monoalkyl-substituted benzenes.

Further evidence of this trend in the spectra may be obtained by comparing the relative intensities of several of the bands in each spectra with the relative intensities in other spectra. It has been stated that the spectrum of a monosubstituted benzene is composed of two sub-spectra (18): One, which is allowed in benzene, is composed of bands involving one of the e_g^+ vibrations (6*b* in Wilson's

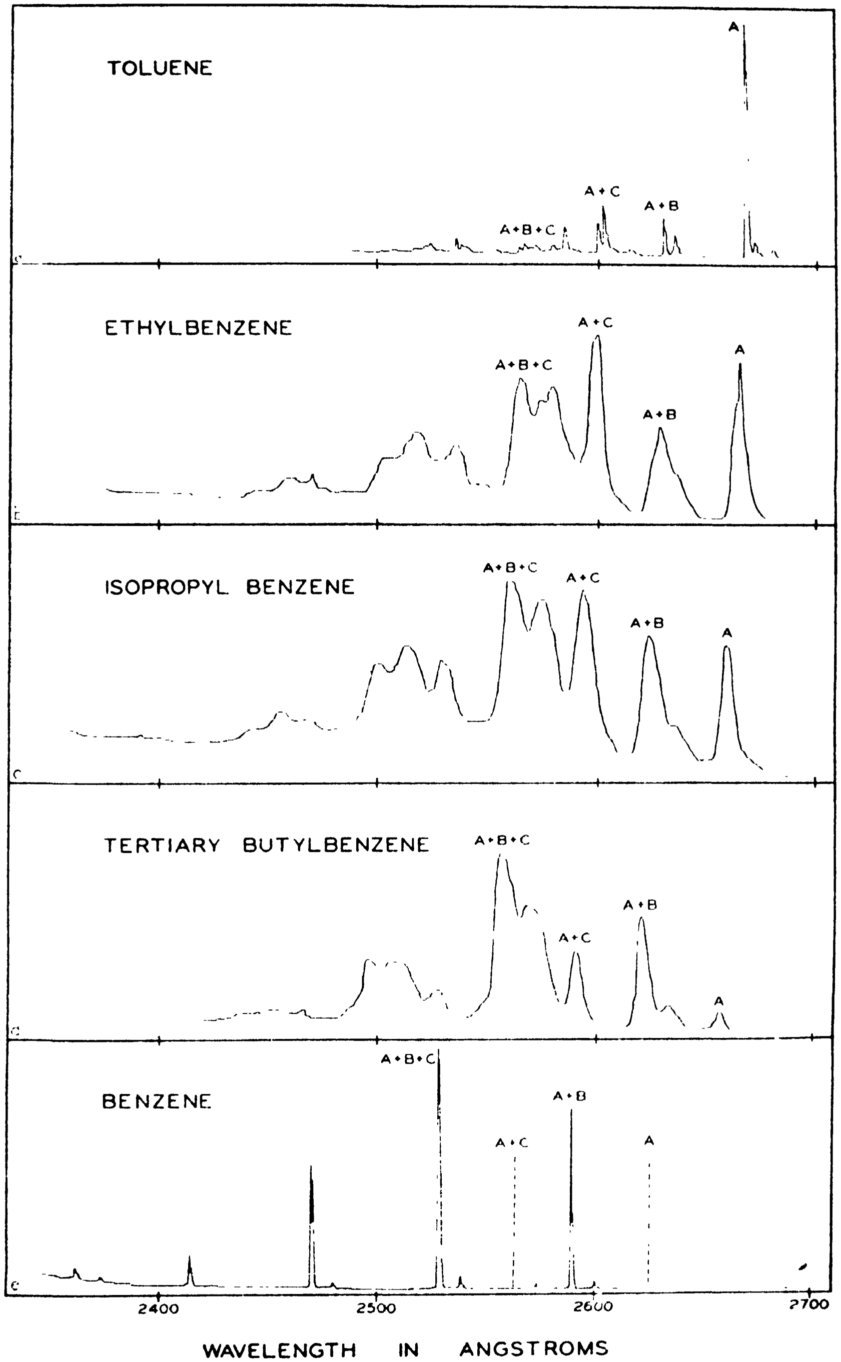

FIG. 3. Microphotometer tracings of the spectra of monoalkylbenzenes. The density scale varies from compound to compound.

notation; frequency, 500 cm.$^{-1}$), hereafter referred to as B. The 0–0 band, hereafter referred to as A, is missing. Thus the benzene spectrum is made up of the following strong bands: $A + B$, $A + B + C$, $A + B + 2C$, etc. (see figure 3e). The second sub-spectrum, which does not appear in benzene, is the one which is made allowed by the migration of electrons into the ring. The 0–0 band, A, appears under these conditions. In addition the vibration C may appear as $A + C$, $A + 2C$, etc. Certain other vibrations which are totally symmetric for the monosubstituted benzenes appear in the same manner as C (see figures 3a, 3b, 3c, 3d). These figures are microphotometer tracings of the vapor-phase spectrographs. The ordinate in this figure is proportional to the intensity of absorption, but the scale from one tracing to another is not comparable, since the exposure of the plate and the sensitivity of the microphotometer were set so as to bring out the optimum contrast.

From the discussion above it is to be expected that compounds with substituents which permit extensive electron migration into the ring will have spectra in which the second or substitution sub-spectrum, A, $A + C$, $A + 2C$, etc., is relatively more intense. It is seen from a comparison of the spectra in figure 3 that this spectrum becomes relatively less intense in going down the series from toluene to *tert*-butylbenzene.[5]

DISCUSSION

The wave-length shift, the variation of intensity of the 0–0 bands, and the internal distribution of intensity all indicate that the migration of electrons from substituent to the ring becomes smaller as the hydrogen atoms in toluene are progressively replaced by alkyl groups. Since the availability of electrons as indicated by the dipole-moment data increases at the same time, this does not seem to be an electrostatic or inductance effect. It seems necessary to postulate that hyperconjugation with the ring decreases as the hydrogens in the methyl group of toluene are successively replaced by alkyl groups. This implies that the electrons in a C—H bond are less localized than in a C—C bond. The formal difference between the two types of bonds is that in a C—H bond a hybridized *s*–*p* orbital on carbon overlaps an *s* orbital on hydrogen, while in the C—C bond a hybridized *s*–*p* orbital overlaps another orbital of the same kind. It is hoped to discuss this problem in more detail in a later paper.

DIRECTING POWER OF ALKYL SUBSTITUENTS

Studies on the relative directing power of alkyl substituents provide confirmation for the interpretation of the spectra presented above. The earliest experiments were concerned with the orientation of electrophilic substituents in the *p*-alkyltoluenes. It was found that the substituent entered predominantly into the position ortho to the methyl group, indicating that the methyl group possessed directing power greater than that of the other alkyl groups. On the basis of these and other experiments Baker and Nathan stated that the electron-releasing power of a methyl group substituted on benzene is superior to that of other alkyl groups, even though the reverse is true when the substitution is on an aliphatic group (19). Recently Deasy (4) has summarized much of the data relative to hyperconjugation in general and the Baker–Nathan effect in particular. More recently de la Mare and Robertson (5) have measured the relative rate constants for the chlorination and the bromination of alkylbenzenes and found them to be in the order methyl > ethyl > isopropyl > *tert*-butyl. Berliner and Bondhus (3) carried out a competitive bromination of toluene and *tert*-butylbenzene and found that the ratio of the monobrominated toluene to the monobrominated *tert*-butylbenzene in the product was four to one. In neither case was the ortho–para ratio determined, so that some question of steric hindrance might be raised. It is believed by both sets of authors, however, that the factor does not affect the qualitative conclusions which can be drawn: namely, that the electron-donating power of an alkyl substituent decreases as the number of hydrogen atoms on the α-carbon atom is decreased, giving further evidence for the Baker–Nathan effect.

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[5] These data may be taken as evidence for the existence of two sub-spectra in monosubstituted benzenes.

Thus the spectroscopic and chemical data are in accord. Since the spectroscopic data parallel the chemical data so closely, even with regard to small effects of the type discussed here, one is led to the conclusion that the excited state produced in aromatic compounds by the absorption of light must resemble in a number of ways the transition state for the substitution reactions.

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ELECTRONIC TRANSITIONS IN TRISUBSTITUTED BENZENES IN THE NEAR ULTRAVIOLET[1]

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The structure of the near-ultraviolet absorption spectra of the three trichlorobenzenes and of 1,3,5-trimethylbenzene is briefly discussed. The spectra of the two symmetrical trisubstituted benzenes represent forbidden transitions made possible through the distortion of the ring by unsymmetric vibrations. The spectrum of 1,2,4-trichlorobenzene results from an allowed transition, i.e., a transition moment is present at the equilibrium position of the molecule (migrational moment). The spectrum of 1,2,3-trichlorobenzene belongs also to an allowed transition, according to group theoretical rules. However, calculations (Sklar) show that the contributions from the substituents to the migrational transition moment annul one another in the first order, so that the spectrum takes on features characteristic of a forbidden transition. Characteristic differences among the various spectra are pointed out and a comparison is made with the same spectra in solution.

INTRODUCTION

Spectroscopic investigations of benzene derivatives have been made mostly in solutions. This applies to studies in the ground state—infrared, Raman—and in the excited state—electronic spectra—as well. Most electronic spectra were observed in absorption. Here, complicated compounds have been studied to a larger extent than simple derivatives, probably because of their greater biochemical and biological interest and importance.

In order to furnish the maximum information about molecular structure, the spectra have to be obtained in the vapor state. In the condensed phase the close neighborhood of the molecules causes complications (solvation, hydration, broadening of the individual bands) which are absent or at least less pronounced in the vapor phase.

The great difference between a spectrum in the condensed and in the vapor phase may be seen from figures 1 and 2, which show the near-ultraviolet absorption spectrum of benzene. Each maximum in the solution spectrum is resolved into a whole group of narrowly spaced bands in the vapor spectrum. Note in these figures that the wave-length scale goes from smaller to larger values, i.e., decreasing energies. The numbers at the different groups are wave-number values.

The appearance and intensity of a spectrum depend upon the nature of the electronic states between which the electronic transition takes place. Each transition is accompanied by a characteristic vibrational structure which is fundamentally different for "allowed" and "forbidden" transitions (8, 14). Symmetry considerations and the application of the Franck-Condon principle lead to a number of predictions and statements about the appearance of the spectrum which are very important for the analysis of electronic polyatomic spectra (8, 14). Although these statements seem simple enough, the interpretation of the spectra is often quite difficult. This is partly so because the knowledge of the vibrations of the molecule in the ground state is usually incomplete, and partly because in many cases bands can be interpreted in several

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[1] Presented at the Symposium on Color and the Electronic Structure of Complex Molecules which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago, Illinois, December 30 and 31, 1946.

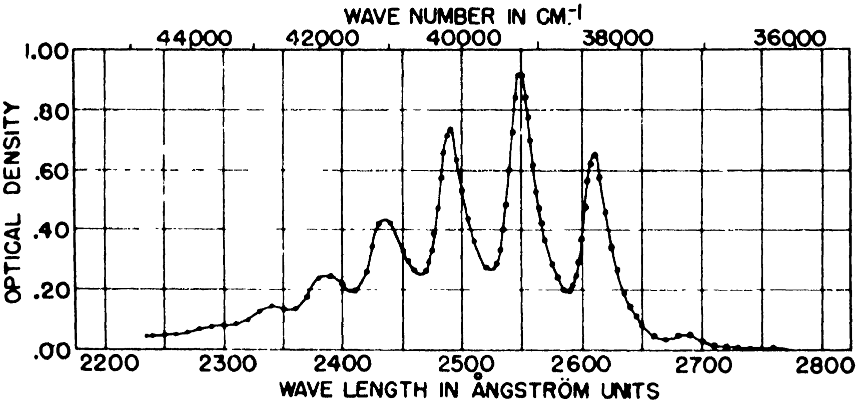

FIG. 1. Absorption spectrum of benzene (liquid solution). Traced from Serial No. 1 of the Catalog of Ultraviolet Absorption Spectrograms (1).

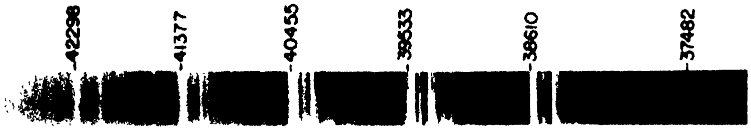

FIG. 2. Absorption spectrum of benzene (vapor).

ways, even to the extent that the ambiguity makes the interpretation meaningless.

If the only aim of the absorption study is the determination of the absorption coefficient and a knowledge of the gross features of the spectrum, then a spectroscopic investigation in solution is entirely satisfactory. It may also reveal whether the transition in question is allowed or forbidden. Small absorption coefficients of the order of that in benzene usually indicate forbidden transitions; larger absorption coefficients belong to allowed transitions.

The gross features of the spectrum may be used to recognize it in other cases, maybe as impurity, but a correct interpretation of the individual maxima will, in most cases, be difficult to achieve. These statements will be amplified from our results on the near-ultraviolet absorption spectra of some trisubstituted benzenes.

EXPERIMENTAL METHOD

The near-ultraviolet absorption spectra of the trichlorobenzenes and of *sym*-trimethylbenzene (mesitylene) were investigated in the vapor phase. Quartz absorption tubes 16, 25, and 75 cm. long and provided with side arms containing the body substances were used. Two separate furnaces regulated the temperature of the main tube and of the appendix, the latter always being kept at a slightly lower temperature than any other part of the tube. In all cases the absorption was studied in dependence on the vapor pressure of the substance.

The 1,3,5- and 1,2,4-trichlorobenzenes were obtained from the Eastman Kodak Company. After the 1,3,5-trichlorobenzene had been recrystallized in methyl alcohol, it melted sharply at 65–65.5°C. The 1,2,3-trichlorobenzene was obtained through the courtesy of the Dow Chemical Company, and the 1,3,5-trimethylbenzene through the courtesy of the Chemistry Department of Duke University. Both substances were very pure samples. All compounds were filled into the absorption tubes by vacuum distillation. Table 1 gives the melting and boiling points of the compounds investigated.

TABLE 1

Melting and boiling points of the compounds investigated

SUBSTANCE	MELTING POINT*	BOILING POINT*
	°C.	°C.
1,3,5-Trichlorobenzene	65.5	208.5
1,2,4-Trichlorobenzene	17	213
1,2,3-Trichlorobenzene	52	219
1,3,5-Trimethylbenzene†	−52.7	164.54 164 66

* Reference 9.

† Reference 15.

Spectrograms were obtained with the Hilger medium quartz spectrograph E_2. It has a dispersion of 14.2 A./mm. at 2950 A., 11.5 A./mm. at 2750 A., and 9.8 A./mm. at 2600 A. An iron arc of the Pfund type was used as source of the comparison spectrum.

RESULTS AND DISCUSSION

The general region of the spectra of the trichlorobenzenes is 2600–2950 A.; that of mesitylene is 2400–2800 A. Previously, the absorption of all four substances was studied in hexane solution (3, 4, 17), but no interpretation was given. Figures 3 and 5 show the solution spectra of the trichlorobenzenes and of mesitylene. The solution spectra show several distinct maxima. A comparison of the absorption coefficients with that of benzene, also taken in hexane solution, shows that, except for 1,2,4-trichlorobenzene, they have very similar small ε values. This may be understood from the theoretical result that the spectrum of 1,2,4-trichlorobenzene represents an allowed transition, while the other two chloro derivatives have forbidden spectra. Of these, the spectrum of 1,3,5-trichlorobenzene is, like that of benzene (6, 11, 13), forbidden for symmetry reasons. The same is true for 1,3,5-trimethylbenzene because of its trigonal symmetry (12). These spectra appear weakly only through the distortion of the ring by unsymmetrical vibrations. The spectrum of 1,2,3-trichlorobenzene, although allowed from symmetry considerations, happens to be forbidden by a cancellation of the contributions of the substituents in the ortho and meta positions to the migrational transition moment (12).

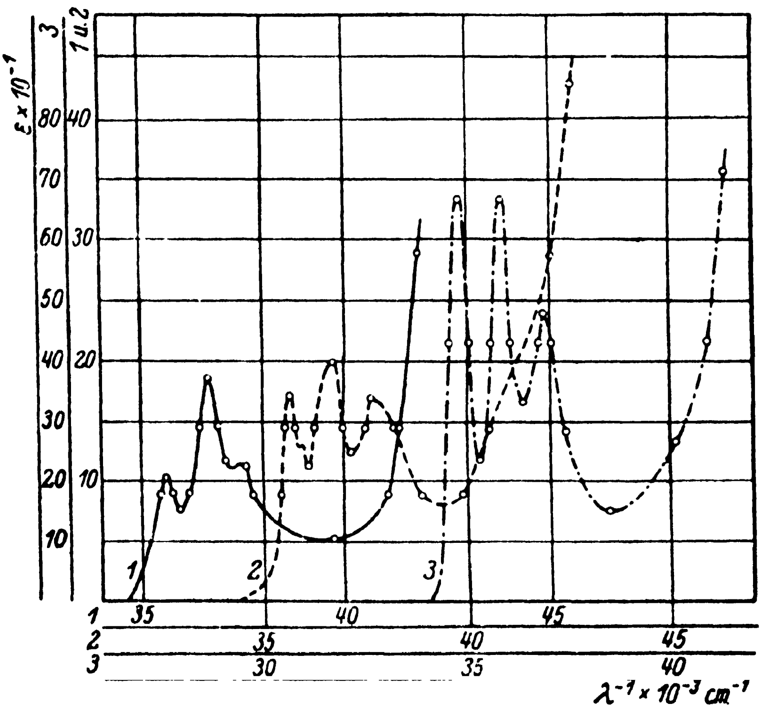

FIG. 3. Absorption spectra of trichlorobenzenes in hexane solution (concentration $7 \times 10^{-4} M$). Curve 1, 1,2,3-trichlorobenzene; curve 2, 1,3,5-trichlorobenzene; curve 3, 1,2,4-trichlorobenzene. (Taken from Conrad-Billroth: Z. physik. Chem. **B19**, 83 (1932))

A proof of these theoretical predictions can be obtained only from the spectra in the vapor phase where structure may be expected. In connection with these predictions and with chemical considerations, it is of interest to observe what particular vibrations will show up in the different spectra.

Figure 4 is a reproduction of the vapor spectra of the trichlorobenzenes. It can be seen that the three maxima or groups of the solution spectra break up into a number of individual bands in the vapor phase. The bands develop with pressure and broaden and overlap each other at higher pressures. A brief discussion will be given for each spectrum separately.

1,3,5-Trichlorobenzene[2]

The bands are not sharp but their degradation towards the red can be recognized clearly. Those bands which appear with sufficient clarity are seen to be doubled with a spacing of about 1.5 wave numbers. Although figure 4 shows only three groups of bands there appears, at higher pressures, a fourth group on the long-wave-length side of the spectrum.

The sixfold symmetry of benzene, D_{6h}, drops to the trigonal group D_{3h} for 1,3,5-trichlorobenzene, and the near-ultraviolet electronic transition A_{1g} B_{2u}

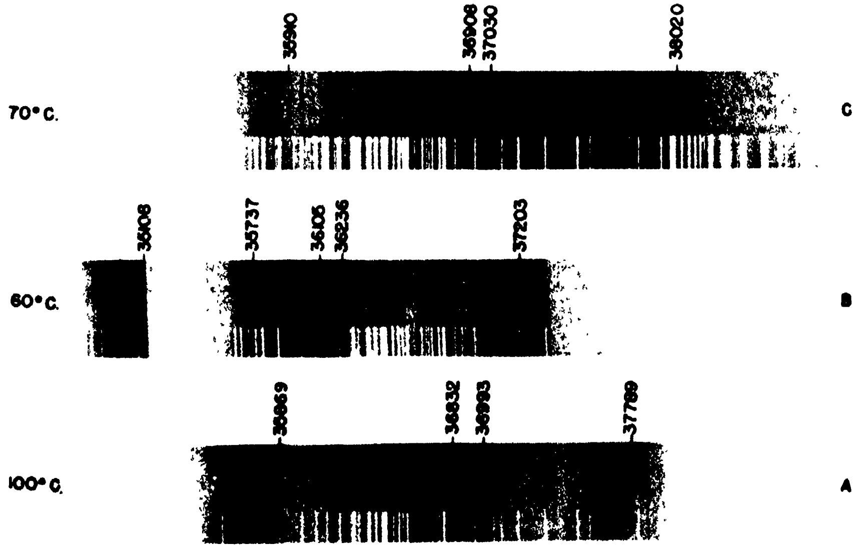

FIG. 4. Absorption spectra of trichlorobenzenes at different temperatures of the reservoir. A = 1,3,5 trichlorobenzene (46 cm. absorption tube), B = 1,2,4 trichlorobenzene (25 cm. absorption tube), C = 1,2,3 trichlorobenzene (75 cm. absorption tube).

of benzene becomes an A_1' A_2' in 1,3,5-trichlorobenzene. The transition is forbidden as in benzene because, as may be seen from group theory, there is no moment connected with it. However, a suitable distortion of the molecule's symmetry will make the production of a moment possible. It can be shown that when an unsymmetric vibration of type ϵ' is singly excited with the electronic transition, a small transition moment is produced and the spectrum will appear with weak intensity. That is, instead of a 0 0 band (electronic transition without vibration) as in allowed transitions there will be a 0 1 band which corresponds

[2] The detailed analysis will be published jointly with Dr. Maurice B. Hall in a contribution to a monograph, *Contributions à l'étude de la structure moléculaire*, which is to be dedicated to the memory of Victor Henri and printed in Belgium.

to a transition from the vibrationless ground state to the upper state in which that particular vibration is excited with one quantum. Superimposed on the 0–1 band should occur the pattern of an allowed band system, i.e., particularly progressions of totally symmetric vibrations. A 1–0 band in which the ϵ' vibration will now be singly excited in the ground state should appear with smaller intensity because of the Boltzmann factor involved.

It was found that the main features of the spectrum conform to theoretical expectations. A difficulty may be expected to arise from the fact that there are seven ϵ' vibrations in 1,3,5-trichlorobenzene as compared to four in benzene, and further that the vibrational frequencies in the ground state of 1,3,5-trichlorobenzene and their assignments to modes of vibration are far less well known than those in benzene. A discussion of the possibilities leads to the reasonably safe conclusion to assign the band 35,869 cm.$^{-1}$ of the first strong group and the very weak band 35,073 cm.$^{-1}$ of the new high-pressure group to 0→1 and 1→0 transitions of an ϵ' carbon vibration of wave number 125 in the ground state and 371 cm.$^{-1}$ in the excited level. The interpretation is supported by the frequent occurrence of a displacement toward the red of 54 cm.$^{-1}$, which is considered as 1–1 transition of this vibration. The non-appearing 0–0 band may be calculated as $35{,}869 - 371 = 35{,}073 + 125 = 35{,}198$ cm.$^{-1}$. The strongest bands in each of the four groups appear in pairs with a separation of 87 cm.$^{-1}$ It probably corresponds to a 1–1 transition of a low non-symmetric vibration. Displacements by 2 × 87 and even 3 × 87 have been found in several places and also superpositions of the 54 difference on the 87 displacements.

The whole pattern of the first strong group is repeated in two subsequent groups. Bands at 36,832 and 36,993 are the first members and the bands 37,789 and 38,123 cm.$^{-1}$ the second members of progressions of the symmetric carbon vibrations 963 and 1122 cm.$^{-1}$ The values in the ground state (5) are 995 cm.$^{-1}$ and probably 1146 cm.$^{-1}$

The bands appearing between the groups are more difficult to explain. There is a possibility that the pair between the first and second groups might result from the excitation of the carbon chlorine valence vibration, but this is not definite.

There is a weak continuous absorption underlying the spectrum. This indicates a dissociation process as a result of the illumination.

1,2,4-Trichlorobenzene

The spectrum of this compound looks entirely different from that of the 1,3,5-isomer. The three maxima of the solution spectrum appear resolved into a large number of almost equally spaced bands of varying intensities. With increasing pressure the bands begin to merge into each other, while new bands appear between the groups and on both wave-length sides of the spectrum. The bands are degraded to the red but, in contrast to those of 1,3,5-trichlorobenzene, most of them are very sharp.

The 1,2,4-trichlorobenzene has the lowest symmetry of the halogenated benzenes, namely C_s. The group provides two kinds of levels only. The only symmetry element is the molecular plane. Hence there are only two types of electronic and vibrational levels which are symmetric or antisymmetric to the molecular plane. The transition is allowed. It is an A'–A', because both the A_{1g} and the B_{2u} states of benzene are symmetric to the molecular plane. From the simplicity of the group theoretical rules, we shall expect a complicated spectrum, because the variety of possible transitions is very large. We should have a strong 0–0 band. Superimposed on it should be progressions of numerous symmetric vibrations and combinations between them. The great number of symmetric vibrations in the unsymmetric compound as compared to the few in the symmetric substance—twenty-one against four—increases greatly the possibility of excitation of strong bands in 1,2,4-trichlorobenzene. On the long-wave-length side of the principal bands we expect a number of v-v transitions and the occurrence of low-lying symmetric vibrations. Indeed, the spectrum of 1,2,4-trichlorobenzene has not only many more bands than the spectrum of 1,3,5-trichlorobenzene but it is also of astonishing regularity. This regularity adds to the difficulty of interpretation.

The band 35,108 on the short-wave-length side of the first group is taken as 0–0 band of the spectrum. Closer inspection of the first and third groups reveals that the pattern of the first group is repeated twice in the third group, involving two symmetric vibrations of wave numbers 997 and 1128 cm.$^{-1}$ Both are quite likely carbon-ring vibrations. The 997 occurs doubly and trebly excited, as well as in combination with the 1128 difference.

The carbon-chlorine valence vibration was found excited in the lower and upper electronic states, forming a progression in the latter state. The appearance of the second group is ascribed to its single excitation in the upper electronic state, giving a wave number of 35,737 − 35,108 = 629 (676 ground-state value (5, 10)).

Many Raman frequencies occur at higher pressures in bands on the long-wave-length side of the 0–0 band. The individual bands in a group which are all about 30 cm.$^{-1}$ apart can be explained only when several independent small vibrations are assumed to be involved in these bands.

The bands become diffuse towards shorter wave lengths and there is some continuous absorption in that region. On the whole, there is much less continuous background in the spectrum of 1,2,4-trichlorobenzene than in the spectrum of 1,3,5-trichlorobenzene.

1,2,3-Trichlorobenzene

The solution spectrum resembles that of 1,3,5-trichlorobenzene more than that of 1,2,4-trichlorobenzene. This applies to strength of absorption and appearance of the maxima as well. The vapor spectrum, on the other hand, does not show much resemblance to either spectrum of the two isomers. It has the weak intensity of the spectrum of 1,3,5-trichlorobenzene but a different structure, and it is much more diffuse than this spectrum. The structure, which consists of three groups of rather regularly spaced bands, resembles somewhat that of the spectrum of 1,2,4-trichlorobenzene, but the two spectra differ markedly in intensity and sharpness of the bands.

The spectrum of 1,2,3-trichlorobenzene is particularly interesting. According to its symmetry the molecule belongs to the group C_{2v} and its near-ultraviolet absorption spectrum should represent an A_1-B_1 transition. This transition is allowed. However, Sklar (12) has calculated that the contributions from the substituents to the migrational transition moment annul one another in the first order. This means that, theoretically, a spectrum will appear only through a vibrational moment, that is, by distorting the symmetry of the molecule through excitation of vibrations. This distortion may be brought about by many vibrations. In reality, the appearance of the spectrum is more that of an allowed transition, since the existence of a 1-0 transition could not be traced, but the intensity is that of a forbidden transition. The groups are apart from each other by about 995 cm.$^{-1}$, which very likely corresponds to a symmetric carbon ring vibration. More work is needed in order to obtain an understanding of the structure of this spectrum.

1,3,5-Trimethylbenzene[3]

The vapor spectrum consists of a number of rather diffuse groups of bands which correspond to the six maxima found in solution. It appears at a pressure of a few tenths of a millimeter and looks almost completely continuous at about 45 mm., while a new group makes a faint appearance on the long-wave-length side. Since motions within the methyl groups of the molecule will hardly influence the characteristic features of the electronic absorption system, these groups are considered as big "atoms" in first approximation and the molecule then belongs to symmetry group D_{3h}. Hence, the transition may be treated as an A_1'-A_2', as in 1,3,5-trichlorobenzene. Figure 6 shows the development of the spectrum at vapor pressures of about 3.5 and 70 mm. of mercury.

The spectrum has a simple appearance. It looks as if a single ϵ' vibration is responsible for its production. This was the conclusion in the case of 1,3,5-trichlorobenzene, and the same interpretation offers an understanding of the mesitylene spectrum. Fortunately, the Raman spectrum of mesitylene is known, together with polarization measurements (7, 16). From a comparison with benzene and 1,3,5-trichlorobenzene we may conclude that the depolarized line at 516 cm.$^{-1}$ corresponds to the 606 ϵ_g^+ in benzene and to the 425 ϵ' in 1,3,5-trichlorobenzene. With this assumption the band 37,000 is taken as the 0-1 band of the ϵ' 516 vibration and the extremely weak band at 36,041 as the corresponding 1-0 transition. The separation between the two bands is 959 cm.$^{-1}$, and it cannot be identified with a Raman line. This is in confirmation of the proposed interpretation. The location of the forbidden 0-0 band may be calculated as $37{,}000 - 443 = 36{,}557$ cm.$^{-1}$ All strong bands appear in pairs, with separations of about 68 cm.$^{-1}$ between them. These are attributed to 1-1 transitions of a low-lying non-symmetric vibration.

The pattern of the first group is repeated more or less distinctly in subsequent groups. They can be explained by means of three different vibrations: 968, 1300, and 555. The first two are very probably symmetric carbon ring vibrations, and the 555 is the $C-CH_3$ valence vibration. It is believed that the

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[3] The detailed analysis will be published in collaboration with Miss Mary Jane Stallcup in a monograph, *Contributions à l'étude de la structure moléculaire*, which is to be dedicated to the memory of Victor Henri and printed in Belgium.

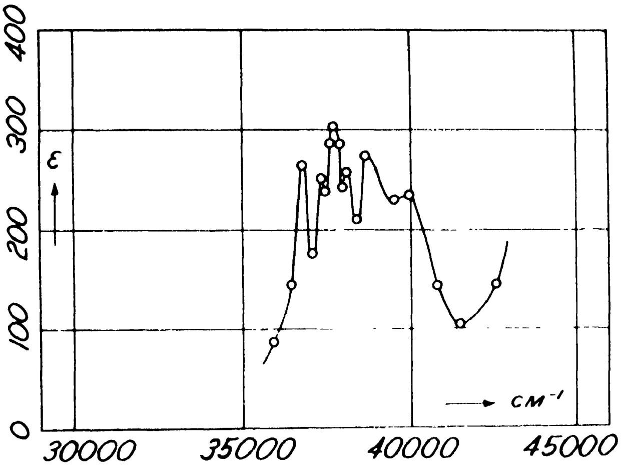

FIG. 5. Absorption spectrum of 1,3,5-trimethylbenzene in hexane solution (concentration $7 \times 10^{-4}\,M$). (Taken from Conrad-Billroth, Z. physik. Chem. **B29**, 177 (1935).)

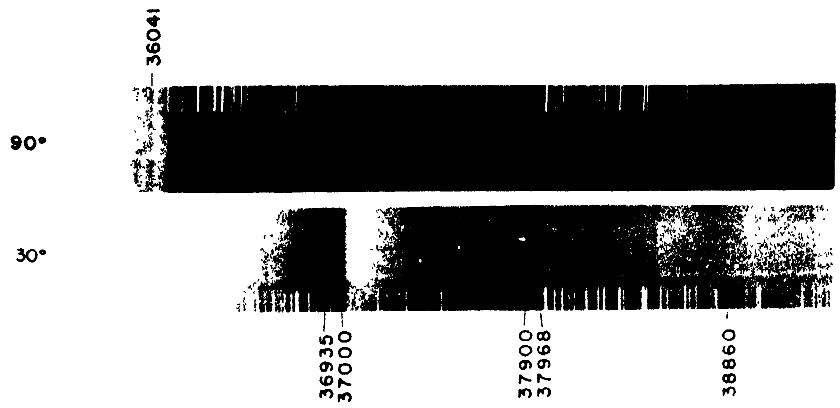

FIG. 6. Absorption spectrum of 1,3,5-trimethylbenzene at different temperatures of the reservoir.

corresponding ground-state frequency is represented by the strong polarized Raman line 575 cm.[1] The three frequency differences occur in progressions and combinations.

The spectrum is much more diffuse than that of 1,3,5-trichlorobenzene.

Comparison of the spectra

A comparison of the spectra may be made with different aspects in mind: as to the spectral position of the groups, as to intensity, and as to appearance (structure and diffuseness). As far as the three trichlorobenzenes are concerned, the general region of the spectra is the same and the different groups in the individual spectra are only slightly shifted with respect to each other (see figures 3 and 4). However, these shifts cannot be compared directly with each other, because the different groups in the spectra do not correspond directly to each other. The first group of the 1,2,4-trichlorobenzene spectrum, which is an allowed transition, contains the 0-0 band (vibrationless electronic transition) in the band 35,108 cm.$^{-1}$ on the short-wave-length side. The first group of the 1,3,5-trichlorobenzene spectrum however, owes its presence to the 0-1 transition of the particular vibration whose excitation makes the otherwise forbidden electronic jump possible. The band 35,869 on the short-wave-length side represents this 0-1 transition with no other vibrations excited. Consequently, what should be compared are the positions of the 0-0 bands of the different spectra, i.e., the observed 0-0 band of 1,2,4-trichlorobenzene should be compared to the calculated 0-0 band of 1,3,5-trichlorobenzene, or 35,108 cm.$^{-1}$ against 35,198 cm.$^{-1}$ In the case of 1,2,3-trichlorobenzene the first weak group contains probably the 0-0 band. Characteristic for forbidden transitions is the absence of a 0-0 band and instead the occurrence of a 0-1 band and at higher pressures a 1-0 band of a particular vibration. In solution spectra the group representing this latter transition is usually too weak for observation, because it is masked by the much stronger absorption of the 0-1 group which is broadened into the region of the 1-0 group. It may be seen, however, in the benzene spectrum of figure 1 in the first small maximum on the long-wave-length side. The 1-0 group is included in the vapor spectrum of mesitylene (figure 6) and cannot be found in the solution spectrum of that substance for the reasons just mentioned (see figure 5). The distance of the weak 1-0 group from the first strong maximum should be different from the separations between successive strong maxima. It is clear from these remarks that comparisons of solution spectra with respect to spectral positions of the maxima should be made with caution in the case of molecules of relatively high symmetry.

As mentioned in the introduction, weak absorption intensities suggest forbidden transitions. From this criterion, they may often be recognized even in solution spectra, as can be seen from figure 3, where the extinction coefficients for 1,2,4-trichlorobenzene are about twice the values of those of the two other isomers. The interesting behavior of 1,2,3-trichlorobenzene has already been noted. The cancellation of the contributions to the migrational transition moment in first approximation works even for substances like 1,3-dimethyl-2-ethylbenzene or 1,2-dimethyl-3-ethylbenzene. Their absorption strength is of the same order as that of mesitylene or benzene, whereas 1,2-dimethyl-4-ethylbenzene and 1,4-dimethyl-2-ethylbenzene are much stronger absorbers. This may be seen from the corresponding series of spectrograms (2). That the attached groups in the mentioned alkylbenzenes are not the same is not as important as the position in which they are substituted. The structure of the alkyl groups will cause only second-order effects in the appearance of the spectra.

The vapor spectra discussed were studied in collaboration with Dr. Maurice B. Hall, Dr. Hedwig Kohn, Miss Mary Jane Stallcup, and Mr. Casimir Z. Nawrocki.

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ELECTRONIC TRANSITIONS IN THE SIMPLE UNSATURATED HYDROCARBONS[1]

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The group of narrow intense bands found in the absorption spectra of all unsaturated hydrocarbons in the Schumann region has been interpreted as the first member of a Rydberg series, the limit of which gives an ionization potential of the molecule. This type of molecular electronic transition is due to the excitation of a π or unsaturation electron of the double bond and is closely analogous to atomic spectra.

The long-wave absorption band which is found in the spectra of all these hydrocarbons is also ascribed to the transition of a π electron and certain characteristics are common to the two groups of bands. In the few hydrocarbons whose spectra show vibrational structure in this region, the pattern is very similar to that in the Schumann region and it is possible to select comparable points for determination of the energy difference between the two electronic levels.

Evidence is presented in support of the interpretation of these long-wave bands as due to an electronic transition which, like the Rydberg transitions, is closely related to atomic spectra. On this basis the energy difference per mole between the two electronic levels would evaluate the difference between two electronic states of the carbon atom in the unsaturated hydrocarbon molecule. These values are given for the molecules whose spectra show sufficient vibrational structure to make the comparison between the two levels unequivocal.

From the heat of hydrogenation and the bond energy for the C—H linkage the heat of the reaction $\underset{|}{H_2C}-\underset{|}{CH_2} \rightarrow H_2C{=}CH_2$ is calculated. The value per carbon atom per mole would give a thermal measure of the energy difference between two electronic states of the carbon atom in the molecule. The results for the four hydrocarbons, containing one, two, and three double bonds, parallel quite closely the energy difference between the two electronic levels as measured from the absorption spectrum of each compound.

According to the proposed interpretation of the electronic bands of the unsaturated hydrocarbons, it is possible to calculate resonance energy directly from the absorption spectrum. The values for benzene and the cyclohexadienes are in satisfactory agreement with those calculated from thermal data, but there is a marked divergence between the thermal and spectral values for cyclopentadiene.

An extensive study has been made in this Laboratory of the absorption spectra between 4000 A. and 1600 A. of thirty-five or more highly purified hydrocarbons, which included aliphatic and cyclic compounds containing one and two double bonds together with benzene and biphenyl. A group of narrow bands found in the spectra of all these hydrocarbons in the region 2200–1800 A. has been identified as belonging to a Rydberg-type transition. The first strong band in each group has been interpreted as constituting the first member of a Rydberg series whose limit is the ionization potential of the molecule (4).

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[1] Presented at the Symposium on Color and the Electronic Structure of Complex Molecules which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago, Illinois, December 30 and 31, 1946.

This assignment was confirmed by the work of Price and collaborators, who determined the photoionization potentials of a number of hydrocarbon molecules (13, 14). In the monoölefins the exact position of the bands, characterized as Rydberg bands, and the ionization potential are dependent upon the number of alkyl groups bound to the carbon atoms of the double bond and are independent of the nature of the alkyl group or groups (5). There is a progressive shift toward the visible as the hydrogen atoms of ethylene are replaced by alkyl groups. That is, the energy of this transition is determined by the immediate environment of the carbon atoms of the double bond and is practically independent of the configuration of the molecule as a whole. This is shown by the striking similarity both in the energy of the electronic transition and in the vibrational pattern between *cis*-2-butene and cyclohexene (6). These spectra are quite closely analogous to atomic spectra, and the electron concerned in the transition is one of the more loosely bound π or unsaturation electrons of the double bond. Another type of molecular electronic transition, characterized by Mulliken (10) as an $N \rightarrow V$ transition, bears no analogy to atomic spectra and has very different characteristics. The identification of these two types of transition in the spectral region below 2300 A. for the monoölefins and in a series of eight aliphatic dienes was made in an earlier publication (2). In the monoolefins and in the dienes with isolated double bonds, the maximum of the very intense continuous band of the charge-transfer type ($N \rightarrow V$ transition) is near 1750 A (57,000 cm.$^{-1}$); where the double bonds are conjugated this band is shifted toward the visible by about 10,000 cm.$^{-1}$, while the narrow bands of the Rydberg transition are not appreciably displaced by conjugation.

In the near ultraviolet between λ 3000 and λ 2300 all unsaturated hydrocarbons show a region of absorption. For those containing one double bond or isolated double bonds, the absorption consists of a broad structureless band of very low intensity which overlaps the more intense band at shorter wave lengths and thus appears as a "stepout" in the absorption curve. Cyclohexene, cyclopentene, and 1,4-cyclohexadiene show this same type of absorption. The curves for the aliphatic dienes, containing conjugated double bonds, show two such abrupt changes of slope, indicating overlapping bands, but it is only in the cyclic dienes and benzene that the spectra of any of these unsaturated hydrocarbons show sharply marked vibrational structure. In the cyclic dienes these narrow bands are superimposed on a fairly intense continuous band (8, 12). The present discussion is concerned only with a possible interpretation of the former.[2]

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[2] That the two bands represent different types of electronic transition seems probable from a comparison of the absorption curves of cyclohexadiene in the vapor phase (8) and in hexane solution. The narrow bands in the solution curve are shifted toward the visible by about 2300 cm.$^{-1}$, while the broad continuous band is shifted about 600 cm.$^{-1}$ Recent measurements in this laboratory of the absorption spectra of concentrated solutions of benzene in different solvents and of pure liquid benzene indicate the presence of a very low intensity continuous band underlying the narrow bands toward the long-wave end. In

The similarity in vibrational pattern between these bands in the near ultraviolet and those identified as belonging to a Rydberg transition is shown in table 1, which gives the band maxima and the separations of the strong bands in each group.

This parallelism in vibrational pattern between the two band systems suggests closely related electronic transitions. If the assignment of the short-wave bands as an $N \rightarrow R$ transition is correct, it would seem reasonable to assume that these corresponding bands in the long-wave region are also due to an electronic transition which is closely related to atomic spectra. Such an interpretation might explain the selective absorption which is shown by chromophoric groups in the molecule,—a type of absorption quite different from that which is associated with conjugation. It is suggested that this atomic-like absorption may represent an excitation which is somewhat analogous to the forbidden transition of the carbon atom, where there is a change in multiplicity and angular momentum but no change in principal quantum number. From this point of view,

TABLE 1

Frequencies and separations of the strong bands in the two electronic levels of 1,3-cyclohexadiene, cyclopentadiene, and benzene

1,3-CYCLOHEXADIENE				CYCLOPENTADIENE			
Band 1 (8)*		Band 2 (3)		Band 1 (12)		Band 2 (14)	
cm.$^{-1}$		*cm.*$^{-1}$		*cm.*$^{-1}$		*cm.*$^{-1}$	
39,797		48,790		38,880		50,380	
41,038	1615	49,970	1515	39,650	1520	50,850	1440
41,412	1647	50,305	1530	40,400	1540	51,820	1460
42,685	1660	51,500	1515	41,170		52,310	
43,072		51 820					

BENZENE			
Band 1 (7)	$\Delta\frac{1}{\lambda}$	Band 2 (3)	$\Delta\frac{1}{\lambda}$
cm.$^{-1}$	*cm.*$^{-1}$	*cm.*$^{-1}$	*cm.*$^{-1}$
37,495		49,035	
	1130		935
38,625		49,970	
	924		880
39,549		50,850	
	920		840
40,469		51,690	
	922		790
41,391		52,490	
	919		740
42,310		53,220	

* Reference number.

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chloroform solution this band shifts to shorter wave lengths, while the narrow bands show a definite shift toward longer wave lengths.

the long-wave group of bands in these hydrocarbons would represent an electronic transition in which one of the unsaturation electrons changes spin, thus giving a triplet state as the excited state. The low intensity in comparison with the Rydberg transition would be in accord with such an assumption. Mulliken has suggested (11) that in the $N \rightarrow R$ transition there is the transfer of one electron to a $3s$ orbital. If then there are comparable points of reference in the two band systems, the energy difference between the two electronic bands should evaluate the difference in energy between two electronic configurations of a carbon atom in an unsaturated hydrocarbon molecule.

Although, as has been pointed out, the position of the bands in the $N \rightarrow R$ transition for a large number of hydrocarbons has been measured with sufficient accuracy for such calculations, only the cyclic dienes and benzene show the sharp vibrational structure in the long-wave band which is necessary for an accurate

TABLE 2

Differences between corresponding bands in the two electronic levels of ethylene, 1,3-cyclohexadiene, benzene, and cyclopentadiene in cm.$^{-1}$ and in kilocalories per mole

HYDROCARBON	BAND 1	BAND 2	$\Delta\frac{1}{\lambda}$	$\Delta Nh\nu$	REFERENCES
	cm.$^{-1}$	*cm.$^{-1}$*	*cm.$^{-1}$*	*kcal.*	
Ethylene	48,330	57,340	9,010	25.70	(13, 15)
1,3-Cyclohexadiene	39,797	48,790	8,993	25.64	(3, 8)
Benzene	38,625	19,970	11,345	32.33	(3, 7)
Cyclopentadiene	38,880	50,380	11,500	32.78	(12, 14)

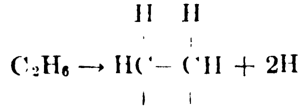
determination of this energy difference. Selective absorption in this spectral region has long been recognized as characteristic of the C=C linkage, but in most molecules the band is continuous and appears only as a stepout in the absorption curve. Measurements by Snow and Allsopp (15) for ethylene show a group of very shallow abrupt stepouts at the short-wave end of a broad "shelf." The breadth and separation of these narrow bands would indicate a possible relationship to the bands identified by Price (13) as the first member of a Rydberg series for the ethylene molecule. The first of these bands, as measured by Snow and Allsopp, is taken as the point of reference for comparison with the band identified by Price as the 0-0 transition in the $N \rightarrow R$ transition. Table 2 gives the values for the four hydrocarbons for which measurements in both the long-wave and short-wave regions are available. All values are for vapor-phase measurements.

Measurements for 1,4-cyclohexadiene have been made in this Laboratory but are not included in table 2 because of our difficulty in obtaining this hydrocarbon completely free from traces of benzene and 1,3-cyclohexadiene. These impurities were discernible only in the long-wave region, where there is a broad stepout whose intensity is of the same order as that in cyclohexene. It is significant, however, that at the short-wave end of this stepout, beginning at about 43,000 cm.$^{-1}$, there is a group of shallow but very sharp stepouts quite similar to those of ethylene but displaced by about 5000 cm.$^{-1}$ In the Schumann region, where the absorption of the 1,4-diene is very intense, there is no evidence of either benzene or the 1,3-diene, and a group of very sharp bands beginning at 51,950 cm.$^{-1}$ is undoubtedly characteristic of 1,4-cyclohexadiene. This gives an energy difference between the two electronic excitations of 25.51 kcal. (8950 cm.$^{-1}$). It should be emphasized that in all of these spectra there seems to be the superposition of two different types of bands in the long-wave region. Only in the conjugated cyclic dienes is the continuous band of high intensity.

The absorption curves of the conjugated aliphatic dienes show two distinct stepouts in this spectral region, but the present discussion is limited to the few molecules in which there is clearly defined vibrational structure, so that the comparison with a corresponding band in the $N \rightarrow R$ transition may be unequivocal.

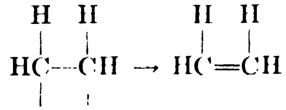
Some years ago attention was called to a relationship between the energy of these two electronic levels and the heats of combustion of saturated and unsaturated hydrocarbons containing the same number of carbon atoms,[3] but no theoretical reason for the existence of such a relationship could be advanced and both spectral and thermal values were of such doubtful accuracy that the paper was not published. With the accurate spectral measurements of the unsaturated hydrocarbons in the short-wave region and the accurate determination of the heats of hydrogenation of these hydrocarbons (9), the correlation of spectral and thermal data has been reconsidered. If the interpretation of the electronic bands which has been presented is valid, it would be reasonable to expect that there might be a relationship between the values of $\Delta N h\nu$ (table 2) and the energy difference between two electronic states of the carbon atom as evaluated from thermal data. Calculations of the energy change per carbon atom per mole which takes place in the formation of a carbon-carbon double bond have been made from hydrogenation data for each of the compounds, the heat of dissociation of hydrogen, and the bond energy for the C—H linkage. The uncertainty in this calculation is, of course, in this latter value, but inasmuch as most of the recent calculations from thermal data have used Pauling's value of 87.3 kcal., this has been used in calculating the difference in energy between a saturated and an unsaturated carbon atom. The calculation for ethylene is as follows:

$$C_2H_6 \longrightarrow C_2H_4 + H_2 \qquad \Delta H = 32.853 \text{ kcal.} \qquad (1)$$



$$C_2H_6 \rightarrow \begin{matrix} H & & H \\ | & & | \\ HC & - & CH \\ | & & | \end{matrix} + 2H \qquad \Delta H = 174.6 \qquad (2 \times 87.3) \qquad (2)$$

$$2H \rightarrow H_2 \qquad \Delta H = -103.4 \qquad (3)$$



$$\begin{matrix} H & & H \\ | & & | \\ HC & — & CH \\ | & & | \end{matrix} \rightarrow \begin{matrix} H & & H \\ | & & | \\ HC & = & CH \end{matrix} \qquad \Delta H = -38.35 \qquad (1 - 2) - (3)$$

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[3] Paper presented by Emma P. Carr before the Division of Physical and Inorganic Chemistry at the 78th Meeting of the American Chemical Society, which was held at Minneapolis, Minnesota, September, 1929.

By similar calculations, the heats of formation of two double bonds in dienes and three double bonds in benzene have been evaluated from the heats of hydrogenation of these compounds, and the results are given in column 1 of table 3. Column 2 gives the energy change per carbon atom per mole, and for comparison column 3 gives the energy difference between electronic states as calculated from the absorption spectrum.

The values calculated from thermal data (column 2) are all lower than those from spectral measurements. The significance of the results lies not so much in any close agreement but in the parallelism between the two sets of values. This is particularly true with benzene and cyclohexadiene, where the hydrogenation product is the same for both hydrocarbons. There is a much wider divergence between the two values for cyclopentadiene where there are undoubtedly more complicating factors, such as ring strain and lack of constancy of the C—H bond energy, which affect the thermal value. The close agreement between the spectral values for the carbon atom of benzene and of cyclopentadiene may be merely fortuitous, but in the light of the aromatic character of the reactions of cyclopentadiene this result is of particular interest. No value for the heat of hydrogenation of 1,4-cyclohexadiene is available, but it would probably be twice that of cyclohexene, which would give an energy change per carbon atom per mole of 21.3 kcal. The energy difference between the two electronic bands is 25.51 kcal. It should be emphasized that these calculations have been made for *all* the simple hydrocarbons which show sufficiently marked vibrational structure for comparison of the two bands. Values for the alkylbenzenes might be calculated, but heats of hydrogenation and the energy difference of the two electronic bands parallel so closely those for benzene that the results would be practically identical with the values for benzene itself.

TABLE 3

Comparison of energy difference between electronic states calculated from thermal data and from absorption spectra

HYDROCARBON	1	2	3
	kcal.	*kcal.*	*kcal.*
Ethylene	−38.35	19.17	25.70
1,3-Cyclohexadiene	−87.1	21.8	25.64
Benzene	−163.8	27.3	32.33
Cyclopentadiene	−91.6	22.9	32.78

Thermal calculations for ethylene, using the more recent (1) value of 99 kcal. for the C—H linkage of ethane, give an energy change per carbon atom per mole of 30.87 kcal. This value is about as much above the spectral value as the value in table 3 is below. A similar relationship would be shown for the thermal values in the other compounds, but the exact agreement or the disagreement between the two sets of values is less significant than the parallelism in the amount of change from compound to compound. For example, from spectral measurements the difference between cyclohexadiene and benzene (per carbon atom) is 6.69 kcal.; by thermal measurements it is 5.5 kcal. (table 3) or 5.37 kcal., using the higher bond energy.

If the interpretation of these spectra which has been presented is correct, it is possible to calculate the resonance energy of the molecule directly from its absorption spectrum. The energy difference per carbon atom for ethylene, 1,4-cyclohexadiene, and 1,3-cyclohexadiene is closely the same; the greater energy difference between the two electronic levels in benzene (32.33 kcal.), as compared with the corresponding difference in ethylene (25.70 kcal.), would represent a stabilization or resonance energy of 6.63 kcal. per carbon atom in benzene, or six times this amount (or 39.8 kcal.) per mole of benzene. This value is 4 kcal. greater than that calculated from heats of hydrogenation. On the basis of their spectra, neither of the cyclic hexadienes would have any resonance energy, while the spectrum of cyclopentadiene gives a value of 28.3 kcal., as compared with only 4.2 kcal. from heats of hydrogenation. If, however, the aromatic character of a molecule is associated with its resonance energy, the spectral value for cyclopentadiene would seem to be in better accord with its chemical activity.

A number of other applications of the theory that has been proposed are possible, but until the fundamental assumptions are established through the critical analysis of data on the simple hydrocarbons, it is inadvisable to attempt the interpretation of more complex problems.

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ABSOLUTE ABSORPTION INTENSITIES OF ALKYLBENZENES IN THE 2250-1700 A. REGION[1]

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The absolute intensities of absorption of benzene, toluene, ethylbenzene, and the three xylenes, all in *n*-heptane solution in an 0.13-mm. cell, have been measured with a vacuum fluorite spectrograph in the region 2250-1700 A. Each of the curves follows the basic benzene pattern: there is one electronic transition showing diffuse vibrational structure near 2100 A., with molar extinction about 8000 and an oscillator strength about 0.14; and there is another transition with a strong broad continuum peaking near 1900 A., with maximum extinction about 60,000. The total oscillator strength of the two transitions together varies from 0.79 ± 0.08 for benzene (compared to the prediction of 0.71 by Mulliken and Rieke) to about 1.3 for the xylenes. One substituent produces a red shift of about 1700 cm.$^{-1}$ and 40 per cent increase in strength; two substituents, about 2500 cm.$^{-1}$ and 60 per cent. The *m*-xylene spectrum is further to the red than the mean of the *o*- and *p*-xylenes and is more intense than either.

The spacing of the 2100 A. bands is about 950 cm.$^{-1}$, the breathing frequency of the ring. Benzene has the most distinct structure in this region; *m*-xylene has the most diffuse structure here, but shows distinct components in its 1900 A. peak.

INTRODUCTION

We have recently had an opportunity to continue the studies begun earlier at the University of Minnesota on the absolute intensities of absorption of organic solutions in the vacuum ultraviolet (9, 15, 16, 21). The spectra of some fifty additional compounds have been obtained and will be published in the near future as rapidly as the plates can be reduced. Besides the boron compounds already reported (15), these compounds include the six alkylbenzenes discussed in the present paper, some olefins and dienes, a number of heterocyclics, some polynuclear aromatics, several compounds showing steric hindrance effects, some amino acids, sterols, and other compounds of biological interest, some short-lived metal-organic complexes, and a few saturated hydrocarbons containing chlorine, sulfur, and other substituents.

Unfortunately, there was no chance at this time to make a number of improvements in technique which are greatly needed to increase the accuracy of the measurements. The justification for taking advantage of the present opportunity in spite of these deficiencies is that absolute intensity measurements in the important region below about 2200 A. are so scarce that any quantitative measurement, even though crude, represents a great advance in our information on most of the compounds studied.

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[1] Presented at the Symposium on Color and the Electronic Structure of Complex Molecules which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago, Illinois, December 30 and 31, 1946.

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The spectrum of benzene in the vapor phase in the vacuum ultraviolet has been reported by a great many investigators (1, 7, 19, 25) but without quantitative intensity measurements. Quantitative measurements have been made on solutions of benzene in non-polar solvents by Henri and his students (4, 8), but have only reached a lower limit of 1900 A. The intensity of the first very strong transition, near 1840 A., has thus remained undetermined, though the oscillator strength has been predicted semitheoretically (10, 11) from the observed intensities of similar transitions in dienes and ring compounds in the quartz ultraviolet.

The spectra of toluene and xylene in the vapor phase in the vacuum region have been obtained by Price and Walsh (18); the spectra of the xylenes in *n*-hexane solution to 1980 A. have been given by Henri (4); and that of ethylbenzene in cyclohexane solution to 1980 A. has been given by Smakula (24). Otherwise, most previous work on the alkylbenzenes terminates near 2200 A., where the absorption is just beginning to rise strongly.

Of course, benzene and many of its derivatives have been repeatedly measured in the more accessible 2600 A. region, under all sorts of experimental conditions and with many different solvents.

APPARATUS AND TECHNIQUES

The absolute intensities of absorption of benzene, toluene, ethylbenzene, and the three xylenes, all in *n*-heptane solution in an 0.13-mm. lithium fluoride cell, were determined in the region 2250–1700 A. The spectrograph used was a Cario–Schmitt–Ott vacuum fluorite instrument kindly loaned to us by the University of Michigan. The techniques used are the same as those described previously (9, 15, 16, 21).

The measure of absorption intensity used here is the molar extinction,

$$\epsilon = \frac{1}{ct} \log_{10} \frac{I_0}{I}$$

I_0 being the initial intensity, I the final intensity, c the concentration in moles per liter, and t the cell thickness in centimeters.

For benzene, the extinctions determined from different plates were consistent, and the mean values given here are believed to be accurate, to better than ±10 per cent. The consistency was poorer for the other compounds, with the uncertainty increasing to ±20 per cent for the xylenes. The reliability may be less below 1800 A., where the corrections for scattered light in the spectrograph become considerable.

For the xylenes, the intensities in the 2100 A. bands were determined from only one selected plate apiece, but the remainder of the curves given here were determined on from two to five plates at every point.

With diffuse solution spectra which show no structure, our measurements are usually made at 2260, 2230, 2200, 2160 A., and so on. However, in the present compounds, maxima and minima could be observed in the bands. These were located by visual inspection to 2 or 3 A. The plates were then photometered at these positions also, so that the fluctuations shown on the curves here were determined with a relative accuracy which seems to be better than ±5 per cent for neighboring bands. The fluctuations are not far from the limit of visual and instrumental discrimination. Some of the maxima observed visually were not justified by the photometry and are marked with a question mark in the tables, but may nevertheless correspond to real components observable visually by virtue of the St. John effect.

SOURCE AND PURITY OF COMPOUNDS

The benzene and alkylbenzenes which were studied were samples of API-NBS hydrocarbons. These were made available by the American Petroleum Institute and the National Bureau of Standards through the A. P. I. Research Project 44 on the "Collection, analysis, and calculation of data on the properties of hydrocarbons." The samples were purified at the National Bureau of Standards by the A. P. I. Research Project 6 on the "Analysis, purification, and properties of hydrocarbons," under the supervision of Frederick D. Rossini, from materials supplied by the following laboratories:

Benzene and toluene, by the A. P. I. Research Project 6. Final purity: benzene, 99.94 ± 0.03 mole per cent; toluene, 99.95 ± 0.02 mole per cent.

Ethylbenzene, by the Monsanto Chemical Company, Dayton, Ohio, through the courtesy of G. Åkerlöf. Purity, 99.86 ± 0.05 mole per cent.

o-Xylene, by the Standard Oil Development Company, Elizabeth, New Jersey, through the courtesy of William J. Sweeney. Purity, 99.990 ± 0.007 mole per cent.

m- and *p*-Xylenes, by the A. P. I. Research Project 45 on the "Synthesis and properties of hydrocarbons of low molecular weight" at the Ohio State University, under the supervision of Cecil E. Boord. Purity: *m*-xylene, 99.86 ± 0.03 mole per cent; *p*-xylene, 99.94 ± 0.03 mole per cent.

SPECTRA

Each of the alkylbenzene spectra shows the same basic benzene pattern: there is a strong allowed electronic transition, designated as the $N \rightarrow V$ transition by Mulliken and Rieke (10, 11), which is characterized by an almost featureless continuum with a peak near 1900 A.; and there is a weaker transition, which is believed to be a forbidden transition in benzene (3, 22), characterized by a rather flat absorption curve with some diffuse vibrational structure near 2100 A.[3]

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[3] *Note on nomenclature of bands:* The upper electronic state of the 2100 A. transition in benzene is designated as ${}^1B_{1u}$ (3,22), that of the 1840 A. transition as ${}^1E_u^-$; but the corresponding levels cannot be called by these same symmetry labels in the other compounds, since the symmetry is different for each of the alkylbenzenes and is indeed somewhat indeterminate under free or slightly hindered rotation of the substituent groups.

Since the intensities in the two regions are so different, the curves in the vicinity of the allowed transitions have been plotted in figure 1; and in the vicinity of the forbidden transitions in figure 2, on a different scale. Some of the main features of the curves are tabulated in table 1.

The agreement with the older solution measurements is qualitatively good as far as those measurements extend. Gross features, such as the relative red shifts and intensity changes among the xylenes, are confirmed satisfactorily. The *International Critical Tables* (8) peak values for benzene and the xylenes in the 2100 A. bands are 0–10 per cent higher than ours, but Smakula's peak value for ethylbenzene is about 10 per cent lower than ours.

The structure in the present curves is sharper than in the older results. Perhaps it is exaggerated; but, on the other hand, the I.C.T. curves, especially for the xylenes, are shifted to shorter wave lengths as compared with ours by 5–15 A. in the 2050–2250 A. region; and this, together with the indistinctness of the structure, may indicate incomplete separation of the isomers in the earlier work. Smakula's wave-length scale is too cramped to permit comparisons of the ethylbenzene measurements.

A visual estimate indicates that the integrated area under the curves of the 2100 A. band of a given compound would not differ by more than 5 per cent between the older and newer measurements, if carried to the same short-wave-length cut-off in both cases.

The major differences between the different spectra take the form of the familiar red shift of the bands and an increase of intensity in the $N \rightarrow V$ peak with alkylation.[4] The first band of the 2100 A. group and the peak of the $N \rightarrow V$ band shift about 1600 cm.$^{-1}$ to the red with the first methyl substitution. On

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This difference (and ambiguity) in terminology points up quite clearly the inadequacy of the symmetry nomenclature when used alone to describe polyatomic electronic states. The corresponding energy levels involved here in the different compounds obviously have almost identical character with respect to term values, vibrational structure or lack of structure, transition probabilities, and, by inference from all of these, electronic wave-functions. It would be important for our usage and our thinking to have a notation for these states which would *assert* and not deny this identity These levels in the different compounds are probably more alike than many atomic energy levels in different atoms which are given the same notation.

The Mulliken notation has indeed provided uniform letters, E, N, Q, R, V, and Z, meeting this need for a number of states or organic compounds and derivatives absorbing in this region. For example, the state like the benzene $^1E_u^-$ state is the V state in all of these compounds (10, 11) (though it differs in some important respects from the state called V in the ethylenes). But this notation has not as yet been extended to the states analogous to benzene $^1B_{1u}$. And there is unfortunately as yet no systematic way of extending this or any other notation to new states as they are found.

A stop-gap suggestion, which will work for a large number of compounds such as alkyl derivatives of a dominant "parent" chromophore, is to write the correct symmetry notation for the "parent" level in brackets, as $(^1B_{1u})$ and $(^1E_u^-)$ for the levels of all of the alkylbenzenes involved here, following this term by such special notations as may be desirable n the particular molecule under discussion.

[4] See references 6, 17, and 20 for discussion of similar effects in the 2600 A. bands of the alklybenzenes.

Main features of spectra

	BENZENE	TOLUENE	ETHYLBENZENE	o-XYLENE	m-XYLENE	p-XYLENE
A. Forbidden transition						
Onset of absorption*	2,080 A. 48,050 cm.$^{-1}$	2,160 46,300	2,170 46.000	2,190 45,600	2,210 (?) 45,200	2,225 45,000
Peaks of component bands	49,000 49.800 50.900 51,700 (?)	47,300 47,800	47,000 48,000 48,900	46,500 47,400 48,500 49,500 (?)	46,200	46,000 47,200 48,000(?)
Maximum molar extinction (ϵ_{max})	6,900	8,100	7,400	8,100	10,500	8,100
Remarks	Components most distinct				Components most diffuse	Narrow irregular maxima
Approximate oscillator strength, f' (to arbitrary cut-off, see text)	0.10 (1950 A.)	0.12 (2000 A.)	0.11 (2000 A.)	0.11 (2040 A.)	0.18 (2030 A.)	0.14 (2030 A.)
B. Allowed transition						
Peak	1,835 A. 54.500 cm.$^{-1}$	1,885 53,000	1,890 52,900	1,905 52,500	1,930 51,800	1,925 52,000
Maximum molar extinction (ϵ_{max})	46.000	55,000	57,000	59,000	76,000	62,000
Components	53,700 (?) 54.500 55,400 (?)	52,400 (?) 53,300 (?)	52,000 (?) 53,200 (?) 54,300 (?)†	†	51,000 51,800 52,800†	51,300 52,500 53,800 (?)†
Remarks	Components doubtful			No components	Components distinct	
Total oscillator strength, f	0.79	1.09	1.11	1.22	1.46	1.23

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* Probably the 0-0 band, except in benzene.

† Curves flatten out at 1750 A., with ϵ about 18,000, before the next absorption. The *m*-xylene curve has an actual peak at 1730 A. with $\epsilon_{max} = 19,000$.

replacing methyl by ethyl, there seems to be an additional shift to the red of perhaps 200 cm.$^{-1}$, but this is not certain; the toluene and ethylbenzene curves coincide within experimental error at almost every point. On adding a second methyl to toluene, a further red shift of about 900 cm.$^{-1}$ occurs, subject to some variation among the xylenes.

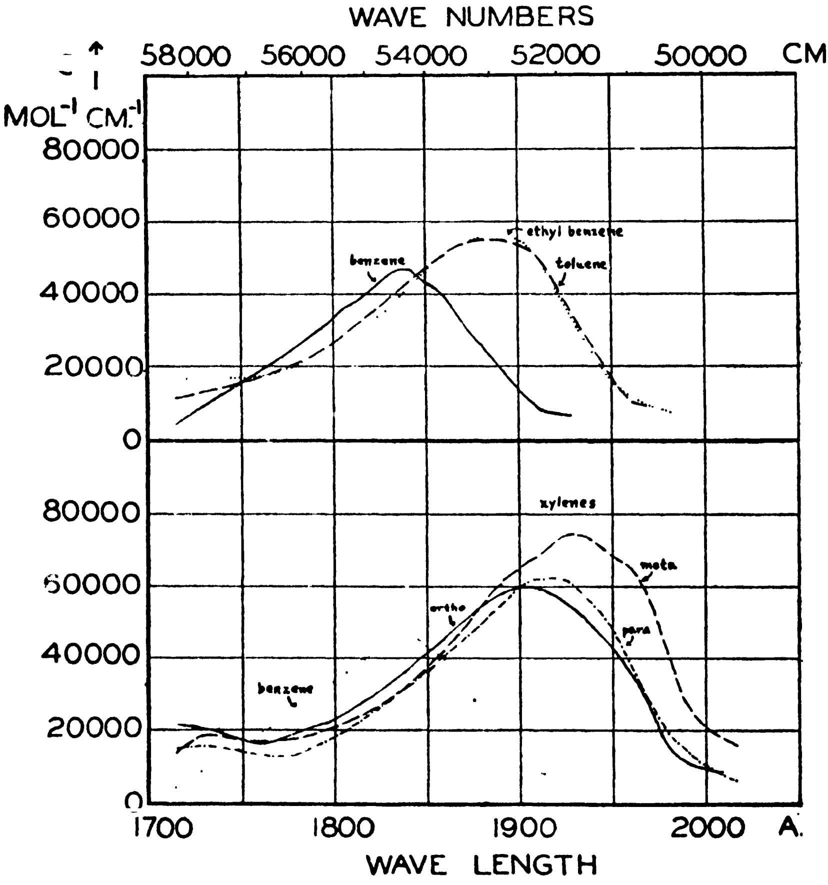

FIG. 1. Transitions near 1900 A. in alkylbenzenes

The first substitution increases the $N \rightarrow V$ peak intensity of benzene about 20 per cent; and it increases the total area under the curve, which is the index of the oscillator strength of the transitions, by 40 per cent. The second substitution produces roughly an additional 20 per cent increase in both quantities.

These shifts of band position and intensity in going from toluene to the xylenes are of about the same size as those found in going from a singly substituted ethylene, such as 1-octene, to a doubly substituted one, such as *cis*- or *trans*-2-octene (14). For the *cis* form, the red shift is 1800 cm.$^{-1}$ and the intensity increase is 0 per cent; for the *trans* form, 1000 cm.$^{-1}$ and 20 per cent. (The more extensive data of Carr and Stücklen on the polymethylethylene vapors (2) cannot be used in the comparison, because the shifts with alkylation in the vapor phase seem to be much larger than those in solution.)

The changes in position and intensity in the $N \rightarrow V$ bands with substitution throw light on the related changes of intensity found in the 2600 A. bands of the alkylbenzenes.[4] In benzene, the latter bands are forbidden, but still occur weakly because of perturbations of the Herzberg-Teller type by which they "steal" intensity from the $N \rightarrow V$ transition (10, 11). The intensity acquired by means of this mechanism should be proportional to the $N \rightarrow V$ intensity itself, and inversely proportional to the square of the separation of the upper states.

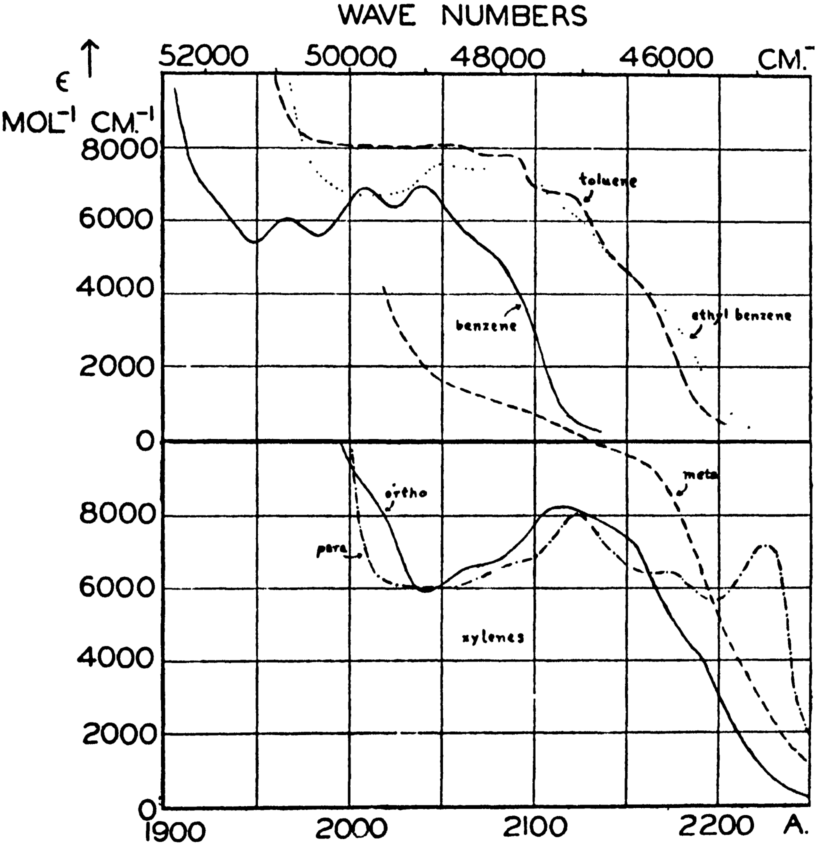

FIG. 2. Transitions near 2100 A. in alkylbenzenes

Now in going from benzene to the substituted benzenes, the present measurements show that the $N \rightarrow V$ intensity increases and the separation of the upper states decreases. There should result considerable increases of intensity in the 2600 A. bands of these compounds from this cause alone, even if all the other parameters affecting the perturbations remained constant.

Thus, in going from benzene to toluene, the $N \rightarrow V$ changes should produce an increase of intensity in the 2600 A. bands by a factor of 1.5; in going to *m*-xylene, a factor of 2.2. Experimentally, the increases are by factors of 2.0 and 2.9, respectively (23); the discrepancies are scarcely larger than experimental error.

Theorists have made much out of these changes of intensity in the 2600 A. bands, attributing them to breaking down of the selection rules by loss of symmetry, to charge migration, and so on. In the case of *p*-xylene these additional considerations may be necessary, since the 2600 A. changes of intensity are much greater than can be accounted for solely by the $N \rightarrow V$ changes. But for the other compounds it appears that the $N \rightarrow V$ changes must first be explained, and after that the 2600 A. changes will largely follow without further assumptions.

This emphasizes the remarks on the symmetry notation made in a footnote above. The surprising thing is not that the loss of symmetry with substitution breaks down the selection rule of the 2600 A. bands and makes them "more allowed," but rather that the breakdown is in most cases so very small.

VIBRATIONAL STRUCTURE

The vibrational components which are seen in the 2250–1700 A. region are very diffuse and symmetrical, and in appearance are not at all like the narrow and strongly shaded 2600 A. bands of these compounds.

Nevertheless, there are differences between the various curves as regards the distinctness of these components. The differences seem not to depend on the extent of alkylation, but rather to be correlated with the symmetry. Thus, the most distinct structure in the 2100 A. bands occurs in benzene, and the next most distinct in *p*-xylene, but the most diffuse is in *m*-xylene. In the $N \rightarrow V$ bands, on the other hand, the clearest components occur in *m*-xylene, next clearest in *p*-xylene, and after that in benzene; and the other components suggested for these bands in table 1 may be imaginary. Diffuse components have been indicated for the $N \rightarrow V$ band of benzene in the vapor phase in some previous reports (1). (In benzene in the vapor phase, very sharp absorption bands with vibrational structure are also seen overlying this $N \rightarrow V$ band. These are regarded as members of a Rydberg series (1, 19). No such bands were found in the present work. Probably they are smeared out in solution, because their Rydberg electronic orbitals are so large.)

A complete explanation of these changes in distinctness among the spectra would require information on the strength and overlapping of all of the strong vibrational series which must be present. Since such information is not available, one can only say that the frequency which dominates the spacing of most of the observed bands is about 950 cm.$^{-1}$ and is the same within experimental error as the totally symmetric benzene breathing frequency of 920 cm.$^{-1}$ which dominates the 2600 A. bands in all of these compounds. On theoretical grounds the vibrational frequencies in the 2600, 2100, and 1900 A. bands are expected to be about the same, because only one of the six unsaturation electrons is supposed to be excited; its contribution to the binding is small and furthermore is probably about the same in each of the upper states of these transitions.

It is easy to see qualitatively that the structure should be clearest in the most symmetrical molecules, benzene and *p*-xylene, where the breathing vibration is the main totally symmetrical frequency; and it should generally be more obscure in less symmetrical molecules, where other totally symmetric frequencies may produce strongly overlapping bands. This explanation however does not account for the apparent sharpness of the *m*-xylene components in the $N \rightarrow V$ peak nor for the fact that the ethylbenzene 2100 A. structure is as clear as—or, if anything, a little clearer than—the toluene structure.

The 2100 A. *p*-xylene structure seems visually to be more narrow and irregular than that of the other xylenes, just as in the 2600 A. bands, indicating that the same totally symmetric vibrations of this molecule are probably present with about the same relative intensity in both groups of bands.

OSCILLATOR STRENGTHS

Oscillator strengths for the transitions were computed from the integrated areas under the curves, by the familiar equation (11, 13):

$$f = 4.32 \times 10^{-9} \int \epsilon_\nu d\nu$$

where ν is the frequency in cm.$^{-1}$ No correction is made for the effect of solution on the f-values, since it has been shown (5, 12) that, in cyclopentadiene and cyclohexadiene at least, the classical corrections do not fit the data for the allowed transitions, and it is not certain what corrections should take their place.

The values of f' given in the first section of table 1 are approximate oscillator strengths for the 2100 A. bands. They were determined by integrating the areas under the curves up to an arbitrary short-wave-length limit. This limit was chosen to lie in the center of the last clear minimum between the two electronic transitions, when such a minimum existed. Though arbitrary, this procedure is straightforward and definite. It was used because there is no unique way of ascertaining the extent of overlapping of the two transitions; such a notion may even be meaningless.[5]

A quantity of more significance than the strength of each transition is the total oscillator strength, f, of the two transitions together, which is also tabulated in table 1. The 2100 A. bands, like the 2600 A. bands, are supposed to be forbidden in benzene (3, 22), appearing only because of interaction with the $N \rightarrow V$ transition. The same is true, or almost true, for the other compounds, as the similarity of the spectra bears witness. The $N \rightarrow V$ intensity is then divided between these two transitions (a negligible part going into the 2600 A. bands), and their combined oscillator strength is the best measure of what the $N \rightarrow V$ intensity would be if no interaction were present.

This quantity has been computed theoretically by Mulliken and Rieke (11). They apply a correction factor of 0.3 to bring their purely theoretical values into line with observed intensities in the ring dienes, and on this basis predict an oscillator strength of 0.71 for the $N \rightarrow V$ transition in benzene. This agrees within experimental error with the observed value of 0.79 given in the last row of table 1. No calculations have been made on this intensity in the substituted benzenes. It seems surprising for them to have oscillator strengths so much greater than unity. Sklar (23) expected the allowed transition intensities to be very little influenced by non-chromophoric substitutions.

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[5] Some recent unpublished work of Dr. W. C. Price in this laboratory on these same compounds shows that there is usually a clear gap between the two transitions in the vapor phase, which would validate the procedure adopted here.

Part of the large f-number of the alkylbenzenes, as well as the excess in benzene itself over the predicted value, if this excess is significant, may be due to the contributions to the absorption from the first Rydberg series members which lie in this wave-length region. The observed series bands in the vapor (1, 19) are narrow and line-like, but may be strong enough to contribute appreciably to the integrated intensity. No theoretical computations have been made on their oscillator strengths, and no accurate way of measuring their intensity separately has been worked out as yet.

The spectrum of benzene has been compared previously (15) with that of borazole or triborinetriamine, $B_3N_3H_6$, which it strongly resembles.

We are indebted to Professor R. S. Mulliken for helpful discussions of the interpretation of these spectra. Technical assistance was supplied by Howard Carter, Dorothy Iker, and George Rotariu. The work would have been impossible without the extended loan of the spectrograph from the University of Michigan. Grateful acknowledgement is made to the American Petroleum Institute and the National Bureau of Standards for the loan of the samples measured in this investigation.

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INTENSITIES OF ELECTRONIC TRANSITIONS IN ALIPHATIC KETONES IN THE VACUUM ULTRAVIOLET[1]

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The absolute intensities of the electronic transitions at 51,000 cm.$^{-1}$ and 60,000 cm.$^{-1}$ have been measured for the compounds methyl ethyl ketone, methyl isopropyl ketone, methyl *tert*-butyl ketone, diethyl ketone, diisopropyl ketone, and di-*tert*-butyl ketone. It was found that the intensity of the transition at 51,000 cm.$^{-1}$ is decreased when the α-hydrogens in acetone are replaced by methyl groups. The intensity of the transition at 60,000 cm.$^{-1}$ is increased when the hydrogens on one α-carbon are substituted by methyl groups and also increased to a lesser extent when the hydrogens on both α-carbons are symmetrically replaced by methyl groups.

To explain the decrease in the 51,000 cm.$^{-1}$ transition, the effects of polarity, bond angle, and bond length were studied. The combined effects of bond angle and polarity cannot account for the observed decreases. Bond length might explain the observed effects.

It is suggested that the electron exited in the 60,000 cm.$^{-1}$ transition does not come from the C=O group, but possibly is excited from an orbital of the $>$C— group.

Many aliphatic ketones show absorption in the neighborhood of 51,000, 60,000, and 63,000 cm.$^{-1}$, in addition to the well-known absorption near 35,000 cm.$^{-1}$ There is also absorption beyond 65,000 cm.$^{-1}$, where the electronic transitions overlap so that they cannot be resolved at present. We have studied the absolute intensities of the 51,000 and 60,000 transitions in the vapor state of seven ketones in which the hydrogens of acetone have been substituted by methyl in a systematic way. The complete experimental results are reported in the present paper, together with some tentative discussion.

The experimental absolute intensity of a transition can be measured by the f-number, or oscillator strength of the transition. To obtain reliable measurements of this quantity, it is necessary to include all rotational and vibrational levels connected with a given electronic transition (6). It is necessary also that the absorption coefficient be essentially constant over a frequency range larger than is covered by the width of the slit. At the pressures used the absorption spectra of the ketone vapors are truly continuous, except in the cases of acetone and methyl ethyl ketone. Rotational structure is absent in all cases, but in the two cases mentioned groups of unresolved vibrational levels give several broad maxima and minima (quasi-vibrational structure).

The f-number is found in the following way (9): A number of lines from a direct-current, constant-intensity source were photographed, on the same plate, through an absorption tube enclosed by lithium fluoride lenses, with the tube both empty and filled with vapor at an accurately measured pressure. Several exposures were made through the empty tube in which the time of exposure was varied at constant intensity, or in some cases the intensity at constant time was varied by calibrated diaphragms (1). Then one or more exposures were made with the vapor on the same plate. For each line of known frequency a density-log exposure curve was drawn, from which the absorption coefficient was found.

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[1] Presented at the Symposium on Color and the Electronic Structure of Complex Molecules which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago. Illinois, December 30 and 31, 1946.

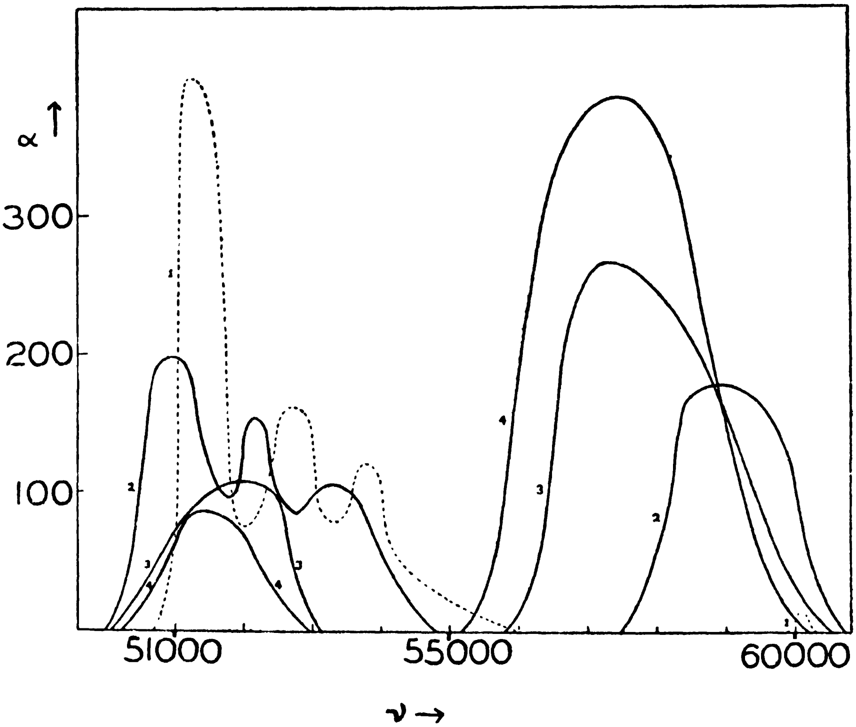

Fig. 1. Absorption curves for acetone (curve 1), methyl ethyl ketone (curve 2), methyl isopropyl ketone (curve 3), and methyl *tert*-butyl ketone (curve 4).

The *f*-number was found by integrating the absorption coefficient over the entire frequency width of the electronic transition. A number of plates were made for each compound in which the pressure was varied from 0.08 to 0.30 mm. The fact was established that the integrated absorption coefficient was independent of pressure. In the case of quasi-vibrational structure, the absorption coefficient was measured at so many frequencies that the contours were revealed in detail.

The absorption curves for the series acetone, methyl ethyl ketone, methyl isopropyl ketone, and methyl *tert*-butyl ketone (unsymmetrical series) are given in figure 1. Curves for acetone, diethyl ketone, diisopropyl ketone, and di-*tert*-butyl ketone (symmetrical series) are given in figure 2. The absorption coefficient α equals $1/l_0 \log_e (I_0/I)$, where I_0 is the intensity of incident light and I is the intensity after passage through a column of absorbing gas of length l_0, measured at 0°C. and 76 cm. pressure, and ν is the frequency in cm.$^{-1}$ The values of f are given in table 1. The experimental values of the dipole moment integral Q are obtained (6) from the relation

$$Q^2\ (\text{exptl.}) = 9.12 \times 10^4 f/\nu_M$$

where ν_M is the wave number of the intensity maximum of the transition.

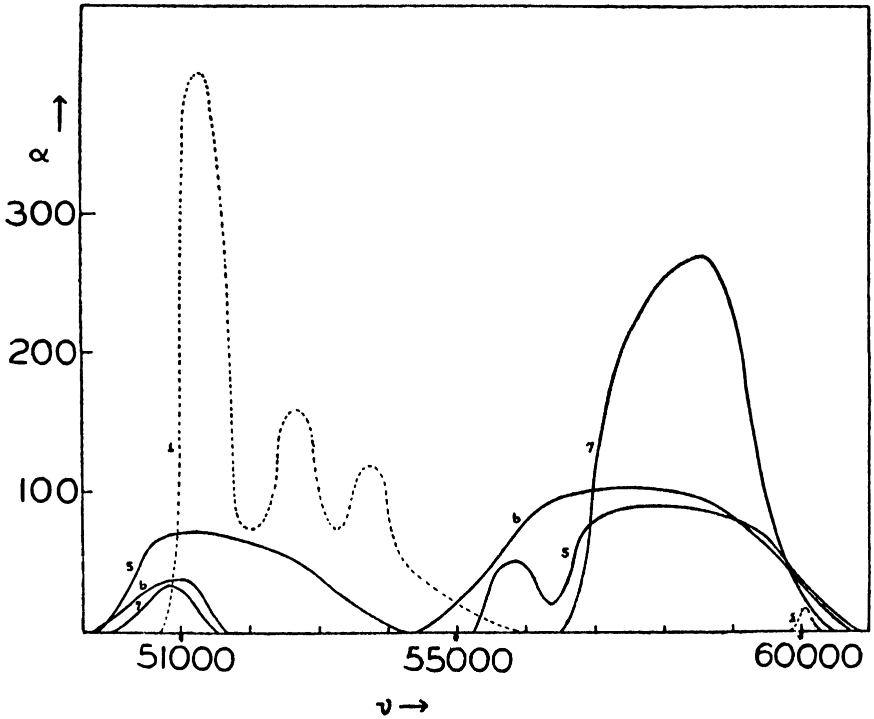

FIG. 2. Absorption curves for acetone (curve 1), diethyl ketone (curve 5), diisopropyl ketone (curve 6), and di-*tert*-butyl ketone (curve 7).

Unless some unexpectedly large error is present, the accuracy of the f-numbers is within 5–10 per cent. The 60,000 transition in acetone is a special case. It is narrow, but apparently weak at the highest pressures. The absorption coefficient can be measured at only one frequency, and so the curve given is schematic. The f-number in this case may be in error by a factor of ten, but it is definitely smaller than any other which we have measured.[2] Substantially the same values of f for the 51,000 transition in acetone, methyl ethyl ketone, and diethyl ketone in solution, which agree closely with these reported values, are given by Platt and Klevens (7).

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[2] The measurements on the two transitions in acetone vapor were made by Miss Martha Lawson (Mrs. N. L. Morse), Dissertation, University of Rochester, 1944.

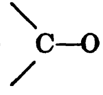
Considerable attention was directed to the purity of the ketones used. Except for di-*tert*-butyl ketone, the starting materials were Eastman Kodak preparations. Acids, oxidizing agents, and biacetyl were removed by washing with dilute sodium bisulfite and sodium carbonate solutions. Samples were fractionated twice in a Purdue-type column, and the final products were taken with a boiling-point range of 0.5°C. or less. The resulting fractions were free of the above impurities.

The di-*tert*-butyl ketone[3] was prepared by the method of Whitmore (10) and purified by fractional distillation. All ketones were freed from air in a vacuum system attached to the absorption tube. In some cases they were fractionated further in the vacuum system.

TABLE 1

COMPOUND	f	ν_M	Q
Transition at 51,000 cm.$^{-1}$			
Acetone	0.020	52,000	0.19
Methyl ethyl ketone	0.018	51,600	0.18
Methyl isopropyl ketone	0.0095	51,600	0.13
Methyl *tert*-butyl ketone	0.0057	51,600	0.10
Diethyl ketone	0.0077	51,700	0.12
Diisopropyl ketone	0.0018	50,800	0.057
Di-*tert*-butyl ketone	0.0016	50,800	0.054
Transition at 60,000 cm.$^{-1}$			
Acetone	0.0002	60,000	0.017
Methyl ethyl ketone	0.014	59,000	0.15
Methyl isopropyl ketone	0.033	58,000	0.23
Methyl *tert*-butyl ketone	0.052	57,400	0.29
Diethyl ketone	0.014	58,000	0.15
Diisopropyl ketone	0.018	57,500	0.17
Di-*tert*-butyl ketone	0.020	58,500	0.18

DISCUSSION

We may suppose that the transition at 51,000 cm.$^{-1}$ arises from excitation of a $2p_{y(O)}$ non-bonding oxygen electron to an antibonding $(t_3 - 2p_{z(O)})$ orbital (3). If it is assumed that the transition remains localized in the C—O group, and that the carbon–oxygen distance has the same value (1.215 A.) as found in formaldehyde by electron diffraction (8), then a change in intensity caused by substitution of hydrogen by methyl can be due to: (*1*) change of angle in the  C—O configuration and (*2*) polarity in the C—O bond. The change of angle was investigated by variation of *s-p* hybridization in the t_3 function. It was found that the limiting values of the hybridization ratio could account for a change in intensity of about 30 per cent. Variation of the polarity coefficients of t_3 and $2p_{z(O)}$ produced smaller changes in intensity, about 10 per cent. If these effects were added, the observed differences in intensity cannot be accounted for.

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[3] Obtained from Mr. C. E. Larrabee, University of Rochester.

Variation of the carbon–oxygen distance would produce much larger effects. There is no direct evidence, however, that this distance is appreciably changed in the substituted ketones. It does not appear worth while to attack the problem quantitatively by use of non-localized orbitals, in view of the complications pointed out by McMurry (4).

Examination of the data shows the following empirical facts, which are offered largely without comment, since their significance, if any, is not obvious at present. The sum of the *f*-numbers of the two transitions is substantially constant in the symmetrical series. In the unsymmetrical series (acetone, methyl ethyl ketone, methyl isopropyl ketone, and methyl *tert*-butyl ketone) the sum of *f*-numbers of the two transitions is not constant, but increases linearly with the number of hydrogens substituted. In the unsymmetrical series, the increase in *f* in the 60,000 transition and the decrease in *f* in the 51,000 transition are very nearly linear. In the symmetrical series the decrease and the increase are exponential for the two transitions.

The equivalent of the 60,000 transition is not found in formaldehyde and acetaldehyde. If the intensity in these molecules is no greater than in acetone, it might not have been observed. Starting with formaldehyde, it appears necessary to substitute three hydrogens by methyl (giving methyl ethyl ketone) to get an appreciable intensity for a 60,000 transition. The data show that the intensity increases much more rapidly in the unsymmetrical than in the symmetrical series.

In contrast with these transitions, the intensity of the transition at about 35,000 cm.$^{-1}$ is unchanged by methyl substitution. This transition is probably to an excited-state configuration . . . $(2p_{y(O)})(x_c - x_0)$ (3) and is confined strictly to the C—O group. We conclude from this that the 60,000 transition is not a second member of the type of transition $N \rightarrow E$.

It is possible that the 60,000 transition arises from a normal-state configuration . . . $(y),^2$ where (y) is an orbital (5) of the $>\!\mathrm{C}-$ group. The form of this orbital will depend on the groups attached to carbon. We shall investigate this possibility, and hope to report later a more satisfactory explanation of these intensities.

Note added in proof: Calculations of the intensity of the 51,000 cm.$^{-1}$ transition have been made in which the C—O bond distance was varied from 1.22 to 2.0 A., by which the intensity could be decreased by 75 per cent. This is sufficient to account for all observed decreases. Calculations were made on the 60,000 cm.$^{-1}$ transition, based on the assumption that the electron was excited from an orbital located in the C—C bond adjacent to the C—O group, lying in the direction of the bond, to a semilocalized orbital perpendicular to this bond. The calculated values of Q are of the correct order of magnitude, and Q increases with methyl substitution roughly in accord with the experimental facts.

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THE CORRELATION OF RESONANCE STRUCTURE WITH ULTRAVIOLET ABSORPTION IN NITRO-SUBSTITUTED ORGANIC MOLECULES[1]

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A semi-historical review is given of the work on the absorption spectra of organic molecules. The classical concepts of auxochromes and chromophores are related to present-day ideas on electronic structure. The ground and excited states of the common chromophores are shown to be similar in configuration. The relative importance of inductive and resonance effects is discussed. The nitroparaffins afford especially interesting examples of the effects of structure on resonance and absorption.

The interpretation of the ultraviolet absorption spectra of complex molecules may be approached from various angles. The calculation of the energies of the electronic levels by the methods of molecular orbitals, for example, is an interesting problem but the difficulties are so great that we cannot hope for much in the way of practical results in the near future.

Sklar (6), Sponer (7), and others have obtained very satisfactory results in the empirical interpretation of the spectral data for benzene and the substituted benzenes in which the substituent is a relatively inactive group. In this interpretation the identification of the vibrational progressions has proved very helpful in distinguishing between allowed and forbidden transitions. It is only in the case of symmetrical structures such as benzene, however, that the vibrational progressions can be recognized. As soon as the symmetry of the benzene molecule is destroyed by the substitution of active groups the vibrational structure disappears and with more complex molecules, particularly in solution, one obtains only continuous absorption and the only observable quantity is the extinction coefficient as a function of wave length. The observer may consider himself fortunate if one or more maxima exist.

With spectra of this sort the most that one can hope for is to identify the absorption with certain active groups in the molecule. There will usually be alternative electronic structures in resonance, including in the excited state at least polar structures in which a carbon atom may have only six electrons with a resulting positive charge or a free pair of electrons with a resulting negative charge. The rules which establish the orthodox structures permissible are quite easily formulated. One does not consider structures which involve the accumulation of excessive charge on one atom or adjacent atoms. A corollary of this is that an electron pair may rotate around an atom as a center but always remains attached to one of the atoms with which it is originally associated.

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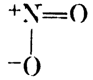
[1] Presented at the Symposium on Color and the Electronic Structure of Complex Molecules which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago, Illinois, December 30 and 31, 1946.

In the absence of more quantitative or more exact theoretical approaches, therefore, it seems worth while to consider what may be accomplished in the way of correlation of absorption with active groups and resonance structures in purely empirical and qualitative fashion.

ACTIVE GROUPS: CHROMOPHORES AND AUXOCHROMES

All atoms show absorption in the far ultraviolet (Schumann region). In this region one obtains an absorption which has been characterized by Mulliken (2) as a Rydberg spectrum. The characteristic absorption of the quartz region is quite different and is to be attributed to electrons which may be regarded as "unsaturation" electrons. Those electrons which are fixed in single bonds are too firmly bound to be affected by wave lengths greater than $\lambda = 2000$ A. Any "active" electrons which produce absorption in the quartz region may, therefore, be assumed to be either electrons in π-type bond orbitals or electron pairs not in a bond. The most important chromophoric groups are

$$C{=}C$$



$$\begin{array}{c} {}^{+}N{=}O \\ | \\ {}^{-}O \end{array}$$

$$C{=}O$$

and are characterized by a double bond in which one bond may be considered to be of the π type, i.e., the electron orbitals are at right angles to the direction of the axis of the two atoms and the electrons are less strongly bound. The characteristic absorption process for these groups is, according to Mulliken, the transfer of both π electrons to one atom ($N \rightarrow V$ transition), a change which results in an ionic bond. In the case of the C=C bond either atom may receive the electrons and become negative, but by the same token the energy required for this process is so great that the absorption lies beyond the quartz region. The weak absorption shown by benzene at 2600 A. has been shown by Sklar to be due to an excitation from the lower symmetric state to the antisymmetric states resulting from the two Kekulé structures. Since the polar states do not enter into this transition appreciably, the dipole strength of the transition is small; in fact, the transition would be forbidden were it not combined with certain vibrations of restricted symmetry.

In the case of groups such as NO_2 and C=O the difference in electronegativity of the two atoms determines the direction of the electron shift and favors this shift, so that the energy of the excited state is lower than for C=C and the absorption shifts into the quartz region. Actually, of course, the π-electron bond may be considered as of mixed covalent and ionic type. In the ground state the covalent type will prevail and the bond will be stabilized by resonance. In the excited state the bond will be approximately the ionic type and will be somewhat less stable because of resonance. The effect of resonance, therefore, is to increase the excitation energy, but the resonance effect will be small unless the covalent and ionic energies are nearly equal, which is not usually the case.

It is thus seen that there are two mechanisms of excitation in benzene that give rise to absorption in different regions. These two mechanisms are fused in the case of more polar groups such as C=O or NO_2 into a single process which combines the essential characteristics of both processes.

AUXOCHROMES

Certain groups when substituted in the benzene ring increase the ease of substitution in the ortho and para positions and also increase the extinction coefficient of the absorption in the quartz region, with usually some shift of the maximum to longer wave lengths. These groups are termed auxochromes, since they generally increase the depth of color when substituted in dye molecules. Typical auxochromes are CH_3, NH_2, OH, and Cl.

It is generally agreed that the effect of these groups is to contribute a negative charge to the benzene ring. This may be pictured as taking place in either of two ways. There may be a slight displacement of charge along the axis of the bond between the auxochrome and the carbon of the ring. This is called the inductive effect. There may actually be a shift of an additional pair of electrons on the auxochrome to form a double bond with the ring carbon and a resultant shift of the π electrons in the benzene ring to give a highly polar quinoid structure. This is termed a resonance effect.

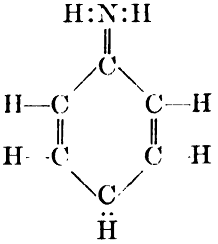
One frequently has difficulty in distinguishing between these two effects, and some writers (4) have sought to explain everything in terms of one effect or the other. It appears that some clarification of these ideas is given by the following considerations:

1. It is always necessary to assume resonance with a polar quinoid structure to account for ortho-para substitution.
2. In the case of the methyl group, no orthodox resonance structure can be written, so that the inductive effect must be assumed.
3. In the case of a group such as NH_2 or OH definite evidence exists for the double-bonded structure, so that the resonance effect must predominate.

It is an interesting fact that two groups as unlike as CH_3 and Cl should behave as auxochromes to about the same degree. Each produces only a slight increase in the extinction coefficient of the benzene absorption at 2600 A. Mulliken has explained the auxochromic effect of the methyl group as being due to hyperconjugation. This appears to be a technical term for what G. N. Lewis was wont to describe as "residual affinity." It appears as a maximum in diborane, where it is difficult to account for the bond between the two halves of the molecule. With chlorine, on the other hand, the inductive effect would presumably oppose the contribution of negative charge to the ring; at least this is the effect observed in the case of chloroacetic acid, where a marked increase in acid strength is to be attributed to the inductive effect. On the other hand, the chlorine atom has electron pairs available to form a double bond, so it must be assumed that the resonance predominates to a slight degree to produce a net auxochromic effect.

In the case of bromine and iodine the auxochromic effect is greatly reduced. The inductive effect will be less certainly reduced, but the predominating resonance effect is likewise decreased since the atoms in the lower rows of the periodic table do not as a rule form double bonds.

In the case of aniline the resonance effect is clearly demonstrated.

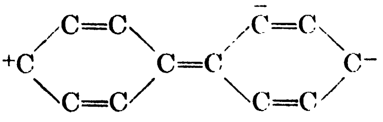


The existence of a double bond is substantiated by experimental evidence for the coplanarity of the NH_2 group with the benzene ring. The great increase in the extinction coefficient of aniline indicates the presence of the polar quinoid form, as is shown in the formula. On the other hand, if one forms the salt such as the hydrochloride the pair of electrons is no longer available to form a double bond and the absorption differs but little from that of benzene itself. The NH_3^+ group, because of the positive charge, has an inductive effect less than that of methyl and in the opposite direction.

It has been shown by Sklar that the electric vector that is active in absorption in the molecules discussed above lies in the plane of the ring and at right angles to the axis of substitution. The dipole strength for this transition cannot be large, and a small value for the extinction coefficient results. If, however, a strongly active (i.e., chromophoric) group is substituted, it may be assumed that the electric vector parallel to the axis of substitution becomes active in absorption and a 100-fold increase in the extinction coefficient may result. In such cases it is not surprising that all trace of vibrational structure disappears. It is with absorption of this type that we are concerned in this discussion.

THE PHENYL GROUP AS AN AUXOCHROME: BIPHENYL

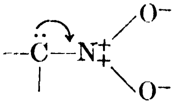
As will be shown in the discussion later, most chromophoric groups behave in a manner exactly opposite to that of an auxochrome, i.e., they behave as if unsaturated and remove negative charge from the ring. In the case of biphenyl, however, the phenyl groups must behave both as chromophores and as auxochromes. This behavior is confirmed by the characteristic ortho–para substitution observed in biphenyl. It was shown by O'Shaughnessy and Rodebush (3) that the strong absorption in biphenyl is only obtained when the rings are coplanar, which means that ionic structures are the important ones, at least in the excited states, since the only structures that can involve both rings in resonance are highly polar. Thus:



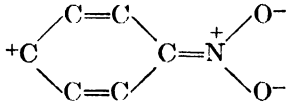
There are, of course, two ortho structures and one para structure for each ring, nine in all, and any attempt to distinguish between different parts of the molecule as auxochrome or chromophore is meaningless, since the electric vector that produces the absorption is the resultant for the whole molecule. The fact that the extinction coefficient for biphenyl is 100 times that for benzene is not surprising when one considers the great polarity of the excited structure. The fact that the maximum absorption is at about the same wave length must be regarded as a coincidence, since there is little resemblance between the excited states in the two molecules.

THE NITRO GROUP AS CHROMOPHORE

Chromophores are typically unsaturated, since they contain π-type bonds. The reason for the unsaturated behavior is that there is always a relatively stable resonance structure possible, in which the π-type covalent bond is converted to an ionic bond. In order for this to happen, however, it is necessary that an additional pair of electrons be supplied to the nitrogen atom. Thus:



If the pair of electrons is drawn from the benzene ring as in nitrobenzene, we have a typical polar quinoid structure:



This structure accounts for the greatly increased absorption of nitrobenzene over that of nitromethane or benzene itself.

NITRO-SUBSTITUTED BIPHENYLS

The symmetrically nitro-substituted biphenyls have been investigated by Williamson and Rodebush (9).[2] Sherwood and Calvin (5) have studied the absorption of some unsymmetrically substituted biphenyls. The results are in agreement with the postulated behavior. Because of the steric interference, the 2,2′-substituted biphenyls depart from the coplanar position and the resonance is destroyed. The absorption is approximately that of two nitrobenzene molecules. 4,4′-Dinitrobiphenyl shows an increased extinction coefficient and shift of the maximum to longer wave lengths, which is to be attributed to the increased polarity of the excited state and the lowering of the energy that is required to produce this state. This effect is still more pronounced in the case of the 4-

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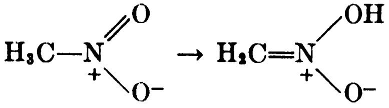
[2] The results reported on 4,4′-dinitrobiphenyl are in error. The compound studied had evidently undergone rearrangement. The absorption of this molecule has recently been studied in this Laboratory, and results will be published. The absorption is very similar to that of 4,4′-dicarboxybiphenyl.

amino-4′-nitrobiphenyl studied by Calvin, where we have a combined auxochromic and chromophoric effect acting in the same direction to stabilize a polar structure.

The case of 3,3′-dinitrobiphenyl is interesting. The absorption observed is about the same as for 3,3′-dicarboxybiphenyl; at the longest wave length the absorption is about the same as that of biphenyl itself, but instead of a maximum at 2600 A. one observes a shoulder with a great increase in extinction coefficient as one goes toward shorter wave lengths. The explanation of this behavior is to be found in the fact that it is not possible to write an orthodox resonance structure involving the chromophoric groups in the 3,3′-position, so that one obtains the absorption of an unsubstituted biphenyl at the wave length 2600 A. There do exist excited structures of much higher energy involving the chromophoric groups, and this gives rise to absorption with a maximum beyond the quartz region which overlaps the biphenyl absorption.

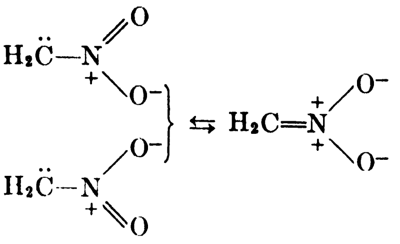
THE NITROPARAFFINS

If there is a hydrogen on the carbon atom to which the nitrogen is attached, as in nitromethane, there is a possibility of a shift of the hydrogen to the aci form



$$H_3C-\overset{+}{N}(=O)(O^-) \rightarrow H_2C=\overset{+}{N}(OH)(O^-) \qquad (1)$$

and in alkaline solution one obtains the negative ion, which has these resonance forms:



Because of the tendency of this anion to polymerize or decompose, the experimental results on its absorption cannot be regarded as established with certainty, but the absorption maximum occurs at somewhat shorter wave lengths than that of nitromethane itself but with an extinction coefficient of the same order of magnitude as that of nitrobenzene. Any correspondence in the absorption of the aci form of the nitroparaffins to that of the nitro forms must be regarded as purely coincidental. On the other hand, the differences in the absorption of nitromethane and nitrobenzene may be attributed to differences in the auxochromic action of methyl and phenyl. Always, of course, one must keep in mind that the absorption is a property of the molecule as a whole and not of a particular group.

The nitro derivatives were the subject of Hantzsch's classic work on the pseudo acids. Hantzsch (1) was able to demonstrate that for phenylnitromethane two crystal forms exist, which he identified with the two forms shown above in equation 1. Recently Turnbull and Maron (8) have attempted to estimate the ionization constants for the two forms in solution.

It was pointed out above that only one form should exist for the ion, which should be a resonance hybrid. This conclusion was in doubt for some years because of the reported persistence of optical activity, but this doubt has now been resolved. As soon as the ion is neutralized, however, one structure or the other must be established and the resonance energy, at least so far as the carbon-nitrogen bond is concerned, must disappear.

Since the nitro form is a very weak acid, the conversion to the aci form in solution of moderate alkalinity is a slow reaction, and the establishment of equilibrium between the two forms may not take place readily. Thus, it may be possible to produce one form or the other in solution by changing the pH regardless of the relative stability of the two forms. It is clear that the aci form would be relatively more stable in aqueous solution than in hexane, for example, but it is not possible to say which is the more stable form. One might expect phenylnitromethane to be more acidic than nitromethane, and it is possible that the stability relations may be reversed for the two derivatives.

The absorption curves for the two forms should be different from each other and from that for the ion. Since the curves for any two forms will probably cross at some wave length, we may expect an isobestic point, and since it is unlikely that the curves for three different forms will cross at the same point we should expect three isobestic points. It should be possible by the study of the ultraviolet absorption in solution to locate these points and to determine the relative amounts of the different forms present in solution and from these calculate the relative stabilities.

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STERIC HINDRANCE TO PLANARITY IN DYE MOLECULES[1,2]

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I. INTRODUCTION

It is possible to account for the color of organic compounds very simply: a compound will be colored when it can exist both in a ground state and in an excited state to which it is capable of being raised by the absorption of visible radiation. Such a statement tells nothing, of course, about the chemical structure of colored compounds, but chemists have evolved theories which correlate structure with absorption, some of those current today being lineal descendants of the old chromophore–auxochrome theory of Witt, greatly extended and expressed in terms of modern electronic concepts, and illuminated and explained by quantum physics.

In considering the absorptions of an array of different compounds from this standpoint, one becomes conscious of the operation of a number of different factors, some outlined fairly clearly, others but dimly, though not all of these are likely to apply in any one instance. The future progress of the study of the relation between color and chemical structure is, in fact, likely to require the elucidation of a considerable mass of detail, the nature of which makes it impossible to codify into a few sentences or even paragraphs.

As an example of a factor which applies in some cases but not in others, one may cite an effect of considerable significance for the numerous dyes with two low-energy extreme resonance structures of *unequal* energy. This is the difference between these energy levels, or the "asymmetry." Considered in con-

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[1] Presented at the Symposium on Color and the Electronic Structure of Complex Molecules which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago, Illinois, December 30 and 31, 1946.

[2] Communication No. 1150 from the Kodak Research Laboratories.

junction with the length of the chromophoric chain, this determines what has been called the "deviation in λ_{max}," that is, the amount by which the absorption differs from that calculated by averaging the values of the two related symmetrical dyes (2). But this effect clearly plays no part in the absorption of the numerous groups of dyes which have two *identical* low-energy extreme structures.

The present paper deals with a factor which, like deviation, is completely lacking in some dyes, those that are planar, but is of great significance for many others, some of which will be discussed in detail.

II. PLANARITY OF DYE MOLECULES

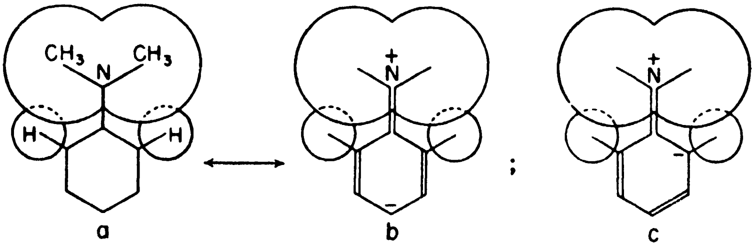
It was pointed out by Pauling (7) that resonance within conjugated systems, whereby all the linkages of the conjugated chain acquire some double-bond character, results in a tendency toward planarity of the atoms involved. The direct experimental evidence for this is not particularly extensive, but includes the determination of the planarity of the molecules of stilbene (9), *trans*-azobenzene (5) and phthalocyanine (10). It has accordingly seemed reasonable to assume that where a scale drawing of a dye molecule shows planarity to be possible, using the accepted interatomic distances, van der Waals radii, and bond angles, then the molecule will be planar, the condition being enforced by the energy of resonance stabilization. Certain dyes contain long polymethine chains =CH—CH=CH— etc., which makes it possible sometimes to draw a large number of *cis-trans* isomers. Not all of these will be planar, and it has seemed plausible to restrict the choice to those that are planar, a line of argument that thus far has not been rigidly proved. In the present paper experimental evidence is for the first time adduced in support of reasoning of this kind (e.g., dye XX).

Thus far, too, relatively little has been done to determine the effect of distortion from planarity on the absorption of a given dye. The present paper is a continuation of work in this direction. The method adopted is necessarily comparative, and definite determinations of the structure of distorted dye molecules by x-ray and electron-diffraction methods still remain to be done.

III. EARLIER WORK ON EFFECT ON ABSORPTION OF DISTORTION FROM PLANARITY IN VARIOUS MOLECULES

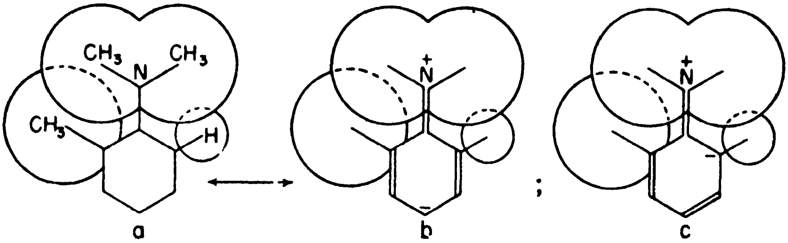
Although the effect of steric hindrance to planarity on absorption has been examined in many substances, few of these are true dyes. Two main types of behavior may be distinguished. The great majority of studies have been made on compounds in which introduction of a "crowding" substituent is made in a molecular type characterized by the existence of a *single* low-energy resonance structure. As a rule, it is not this dominant structure, usually benzenoid, that is rendered less stable by the presence of the crowding substituent, but a higher-energy contributing structure or structures. The energetic asymmetry of the extreme structures of the molecule is thereby increased, and the absorption shifts to shorter wave lengths. Reduction in intensity is shown at the same time, because of the reduced overlap of the electronic orbitals.

Thus, Remington (8) compares the absorption of dimethylaniline (I) with that of dimethyl-*o*-toluidine (II), the drawings of which are approximately to scale.[3]



I

Dimethylaniline



II

Dimethyl-*o*-toluidine

In I there is the possibility of resonance between the uncharged structure Ia and polar structures of the type of Ib and Ic. In Ia the $(CH_3)_2N$— group is linked to the benzene ring by a single bond about which free rotation is permitted, but in Ib and Ic this linkage becomes a double bond, the geometry of which requires the carbons of the methyl groups to be coplanar with the atoms of the C_6H_5— group. The drawings indicate a rather small amount of crowding in this planar arrangement, which can almost certainly be accommodated without departure of the carbons and nitrogen of the $(CH_3)_2N$— group from planarity with the phenyl group.

In II, on the other hand, the *o*-methyl group will undoubtedly crowd the dimethylamino group to a serious extent in the planar arrangements IIb and IIc, resulting in increase in their energy, although in IIa the crowding can be eased by rotation about the N—C_6H_5 single bond, with not much change in energy. The resulting increased separation of the energy levels of IIa and of IIb and IIc relative to Ia and to Ib and Ic results in diminished resonance interaction, but in absorption at shorter wave length of the band corresponding to the particular transition under consideration.

Examples similar to the above are relatively numerous in the literature, but only a single example has been described where crowding substituents were introduced into a compound, a dye, for which two identical low-energy structures could be written. In this case Brunings and Corwin (4) compared the absorptions of the symmetrical ions III and IV.

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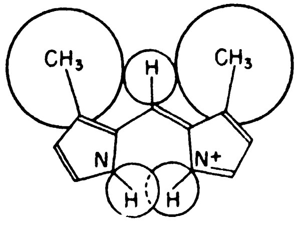
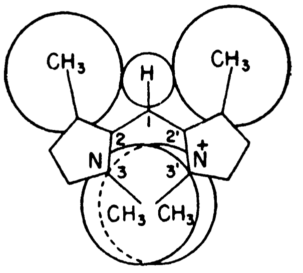
[3] The dimensions used in the drawings in this paper are those listed by Jones (6).



III

λ_{max} = 4730 A. in chloroform
$\epsilon_{max} = 13.5 \times 10^4$



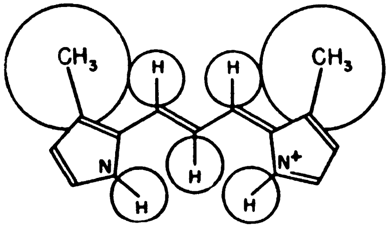
IV

λ_{max} = 5100 A. in chloroform
$\epsilon_{max} = 5.7 \times 10^4$

It was noted that in structure III, which was plausibly assumed by Brunings and Corwin to be the most likely for the compound, the two pyrrole rings could be nearly if not quite coplanar, for the van der Waals radii of the hydrogen atoms attached to the nitrogens overlap, as shown, to an extent that can probably be accommodated with maintenance of planarity by adjustment of bond angles alone. If these hydrogen atoms are replaced by methyl groups, giving IV, planarity is no longer possible if anything like normal bond angles, bond distances, and van der Waals radii are preserved. Brunings and Corwin suggested that the following accommodations could be made: (*a*) increase in the bond angles 1, 2, 2′, 3, and 3′, (*b*) some penetration of the normal van der Waals radii, and (*c*) some departure from planarity. These accommodations, it was suggested, require energy which must be deducted from the resonance energy, a conclusion which requires a *symmetrical* dye such as IV to absorb at *longer* wave lengths than III, and which agreed with the experimental results. Furthermore, such departure from planarity as resulted from the crowding would cut down the overlap of the π-electronic orbitals with consequent reduction of intensity of absorption, and this relationship is to be seen in the curves published by Brunings and Corwin, although it was not specifically referred to by them.

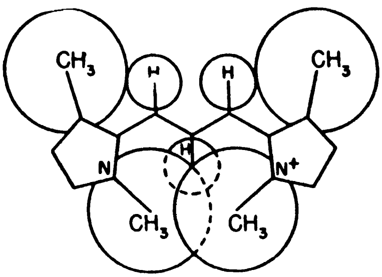
IV. FURTHER STUDIES OF BRUNINGS-CORWIN EFFECT IN CYANINES OF PYRROLE SERIES

One phase of the present work started from this point. The higher vinylogs of III and IV—namely, V and VI, respectively—were first prepared. Because of the longer conjugated chains present in these dyes, the number of possible *cis-trans* isomers is large, but if planarity is to be maintained many of these structures are improbable, and of the various possibilities for the one compound, formula V appears the most probable, while VI is selected from several configurations which are almost equally probable and almost exactly isosteric.



V

λ_{max} = 5950 A. in chloroform
ϵ_{max} = 17 × 10^4

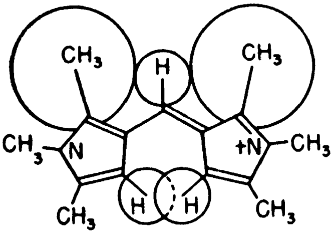


VI

λ_{max} = 5810 A. in chloroform
ϵ_{max} = 17 × 10^4

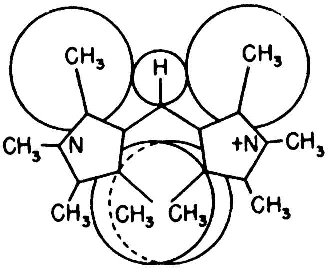
Only very minor adjustments, if any, of bond angles are required to render V comfortably coplanar. In VI, also, the methyl groups do not give rise to anything like the crowding that they do in IV, and in VI planarity can probably be maintained by adjustment of bond angles alone, which would not require much energy. Dye VI would not therefore be expected to absorb at markedly longer wave lengths, nor with markedly lower ϵ_{max} than V, nor in fact does it. Actually it absorbs at distinctly shorter wave length when the absorptions are compared in chloroform, the reason for which is not clear. The maxima are much closer in methyl alcohol, but in this solvent V is extremely unstable, and the value for ϵ_{max} is quite unreliable.

Further confirmation of Brunings and Corwin's viewpoint that crowding a *symmetrical* dye out of planarity results in a shift of λ to longer wave lengths was provided by another set of comparisons to which precisely similar arguments may be applied. Dye VIII, which is crowded from planarity, actually absorbs at markedly longer wave lengths and with greatly lower ϵ_{max} than VII, but between the higher vinylogs, IX and X, there is no such marked difference, the values of λ_{max} being very close and those of ϵ_{max} being of the same order. In this set of four dyes, the absorptions in methyl alcohol were very similar to those in chloroform.



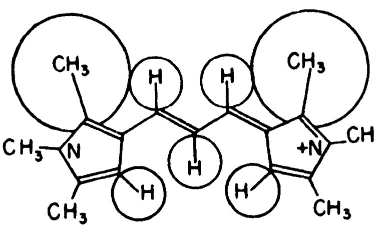
VII

λ_{max} = 4460 A. in chloroform
ϵ_{max} = 3.5 × 10^4



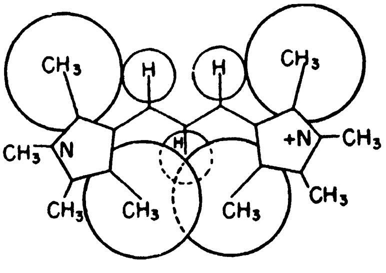
VIII

λ_{max} = 4790 A. in chloroform
ϵ_{max} = 1.25 × 10^4



IX

λ_{max} = 5360 A. in chloroform
ϵ_{max} = 6.3×10^4



X

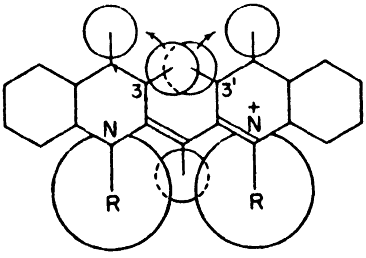
λ_{max} = 5340 A. in chloroform
ϵ_{max} = 7.6×10^4

The fact that the absorptions of VII and VIII differ markedly could not of itself safely be ascribed to the greater size of the methyl groups in VIII relative to hydrogen. It is conceivable that some property of the methyl group other than its mere size might be responsible for the effect, in part if not wholly. However, the close correspondence of the absorptions of IX and X renders this possibility unlikely.

In general, in fact, substitution of an alkyl group for hydrogen in the *nucleus* of a symmetrical cyanine, in such a position that no crowding results, has only a minor effect on the absorption in alcohol. Thus, increases in size of the R alkyl groups attached to nitrogen in dyes XI and XIII produce but slight shifts, and substitution of methyl groups in the 6- and 6′-positions of XIII ($R = CH_3$) to give XXIV is similarly without much effect. The same cannot be said for groups of a decidedly polar character, such as ethoxy and chloro, and for this reason the present studies have been limited to crowding effects produced by alkyl groups, where the electronic effects are minimal.

V. CROWDING EFFECTS IN CYANINES OF QUINOLINE SERIES

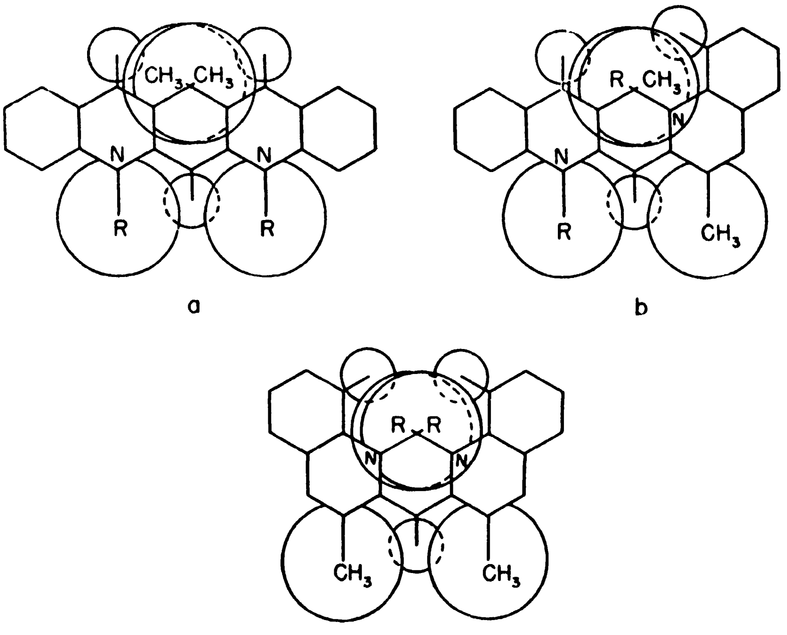
Investigations have also been carried out in the quinoline series, the absorptions of the cyanines XI and XII being compared. The most plausible drawing shows that there is a certain amount of crowding between the hydrogen atoms in



XI

$R = CH_3$ $\begin{cases} \lambda_{max} = 5200 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 7.2 \times 10^4 \end{cases}$

$R = C_2H_5$ $\begin{cases} \lambda_{max} = 5235 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 7.6 \times 10^4 \end{cases}$



a b

c

XII

$$R = CH_3 \begin{cases} \lambda_{max} = 5270 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 4.1 \times 10^4 \end{cases}$$

$$R = C_2H_5 \begin{cases} \lambda_{max} = 5460 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 4.5 \times 10^4 \end{cases}$$

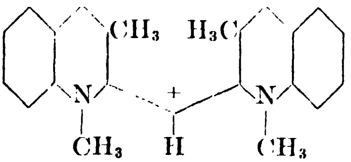
the 3- and 3′-positions of the quinoline rings in XI, but it seems likely that this can be accommodated without substantial departure from planarity by small displacements as indicated by the arrows. In any event, the absorption of the dye in alcohol is very little affected by replacing the *N*-methyl groups by ethyl, although it will be seen later that this type of replacement commonly has a marked effect on a dye molecule that is crowded out of planarity.

In the 3,3′-dimethyl derivative, the three projections for which (XIIa, XIIb, and XIIc) are about equally probable, the crowding is much more pronounced, and all three show marked overlapping of the van der Waals radii of two of the alkyl groups.[4] Furthermore, a result of the hexagonal geometry of the rings in

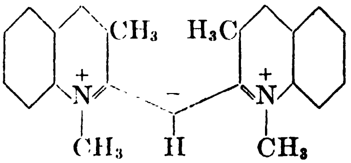
[4] The fact that there are several projections for XII of about equal probability, at least from the standpoint of crowding, raises the possibility, in this and similar cases, of the coexistence in solution of stereoisomers corresponding to several structures. Moreover, even if the choice were restricted to but one structure, let us say XIIa, but the nuclei were twisted out of a common plane, then the molecule could exist in two enantiomorphic modifications. These would be of identical energy and would absorb identically, but the existence of the two different sorts of molecule would very possibly be unfavorable to the close packing which seems to occur in an aggregated state. If, now, the separate structures XIIa, XIIb, and XIIc can exist, then each will be represented by two enantiomorphic modifications, making a total of six distinct molecular species.

XII is to make the overlap greater than in the tetramethylpyrrole derivatives IV and VIII. The Brunings–Corwin effect might therefore have been expected to be greater for XII than for IV or VIII, and it was consequently a matter of surprise that although XII does indeed absorb at longer wave lengths than XI, the shift in λ_{max} is only 70 A., compared with 370 A. for IV (in chloroform) and 330 A. for VIII (in chloroform). However, the intensity of the absorption of XII is significantly below that of XI.

In view of the small shift in λ in passing from XI to XII it seems necessary to invoke arguments in addition to those brought forward by Brunings and Corwin. It might be argued that since free rotation can take place about single but not about double bonds, the linkages of the bridge in a crowded cyanine dye such as XII will tend to become of single-bond character. This results in the favoring of intermediate structures such as XIId and especially XIIe at the expense of other intermediate structures and of the extreme structures. Because of this redistribution of energy levels, a lightening of color could very well result (1), which, largely counteracting a deepening of color due to the causes cited by Brunings and Corwin, could conceivably produce the relationship actually observed.



XIId

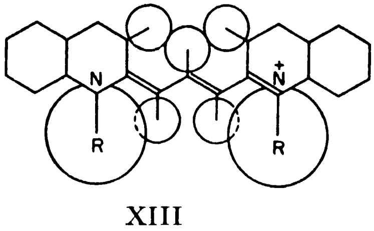


XIIe

Whether this suggestion is valid is at present uncertain, but it should be mentioned that a similar method of approach proved unsatisfactory in dealing with the absorptions of certain dyes (XXIX and XXX) which will be discussed later.

If the methyl groups attached to the nitrogens of XI and XII are replaced by ethyl, the different effects produced are characteristic of each type. As mentioned above, λ_{max} for XI is scarcely affected by the change, the figure for the diethyl dye being only 35 A. different at 5235 A., and ϵ_{max} remains of the same order, the diethyl dye having a value of 7.6×10^4. This kind of behavior is quite generally shown by symmetrical or nearly symmetrical cyanine dyes for which planar structures can be drawn. On the other hand, replacement of the methyl groups attached to nitrogen in XII by ethyl has a pronounced effect on the absorption, λ_{max} being shifted 190 A. to 5460 A., although ϵ_{max} is not much affected. Although it is possible, either in a drawing or a model, so to dispose of the $—CH_3$ groups of the ethyl radicals that the molecule does not appear more crowded, in actual fact replacement of methyl by ethyl appears to increase the effective van der Waals radius of the group, the Brunings–Corwin effect becoming more pronounced.

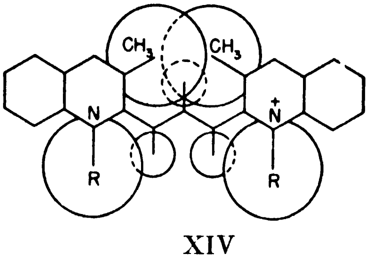
The higher vinylene homologs of XI and XII, i.e., XIII and XIV, were also compared. The drawing of XIII, the most probable formula for the dye, indicates that planarity of the molecule can be attained with only minor adjustment, if any, of bond angles, a conclusion supported by the fact that the alcoholic absorption is virtually unaffected by substitution of the *N*-methyl groups by ethyl. The crowding in XIV is much more severe than in XIII, although decidedly less than in XII. Nevertheless, the shift in λ_{max} of 360 A. in passing from XIII to XIV (both with $R = CH_3$) is much greater than in passing from XI to XII ($R = CH_3$), so that quite obviously there is no simple relationship between a given area of overlap in the projections of these dyes and the shift to longer wave lengths. The considerably lower value of ϵ_{max} for XIV than for XIII is in agreement with the requirements of a distorted molecule for XIV.



XIII

$R = CH_3$ $\begin{cases} \lambda_{max} = 6040 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 18.5 \times 10^4 \end{cases}$

$R = C_2H_5$ $\begin{cases} \lambda_{max} = 6040 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 19 \times 10^4 \end{cases}$



XIV

$R = CH_3$ $\begin{cases} \lambda_{max} = 6400 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 9.7 \times 10^4 \end{cases}$

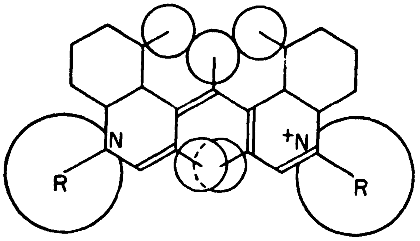
$R = C_2H_5$ $\begin{cases} \lambda_{max} = 6310 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 11.4 \times 10^4 \end{cases}$

One possible contributing reason why less crowding in XIV (relative to XII) produces a greater shift is that the restoring force to any attempted deformation, i.e., the resonance stabilization, is less for the dye of longer chain length (XIV). Another factor may be the readjustment of the energy levels of the extreme and intermediate structures mentioned above.

There still remains the possibility that at least part of the shift in passing from XIII to XIV may be due to some property of the methyl groups in the 3- and 3′-positions other than their bulk, although the considerably reduced ϵ_{max} of XIV indicates distortion from planarity. In this connection it is instructive to consider dye XX, which may be regarded as derived from XIII by insertion of —CH_2CH_2— between positions 3 and 9, enabling planarity to be preserved. This dye (XX) absorbs at markedly longer wave lengths than XIII, so that an aliphatic substituent may, if only rarely, have a strong effect on the absorption, even in the absence of distortion from planarity.

When the *N*,*N*′-dimethyl groups in XIV are replaced by ethyl groups, the effect, surprisingly, is to *reduce* the amount of the shift. The reason for this is not clear, but at any rate this result is quite exceptional and stands alone against a large body of data in which increasing the crowding in an already crowded system intensifies the Brunings-Corwin effect.

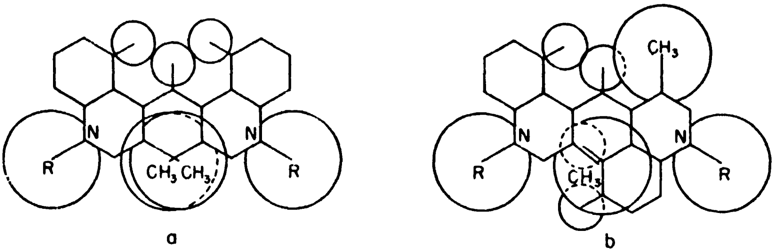
Comparisons carried out in the 4,4′-cyanines XV and XVI gave results in line with the general Brunings-Corwin concept. The 1,1′-dimethyl-4,4′-cyanine (XV) is crowded to an extent that can doubtless be readily accommodated by adjustment only of bond angles. The 3,3′-dimethyl derivative (XVI) on the other hand, is strongly crowded, however it is drawn. We accordingly find that XVI absorbs at appreciably longer wave length than XV (the difference is 255 A.) and with significantly lower ϵ_{max} (5.0 instead of 8.6 × 10^4).



XV

R = CH_3 $\begin{cases}\lambda_{max} = 5885\text{ A. in methyl alcohol}\\ \epsilon_{max} = 8.6 \times 10^4\end{cases}$

R = C_2H_5 $\begin{cases}\lambda_{max} = 5910\text{ A. in methyl alcohol}\\ \epsilon_{max} = 8.8 \times 10^4\end{cases}$



a

b

XVI

R = CH_3 $\begin{cases}\lambda_{max} = 6140\text{ A. in methyl alcohol}\\ \epsilon_{max} = 5.0 \times 10^4\end{cases}$

R = C_2H_5 $\begin{cases}\lambda_{max} = 6150\text{ A. in methyl alcohol}\\ \epsilon_{max} = 5.4 \times 10^4\end{cases}$

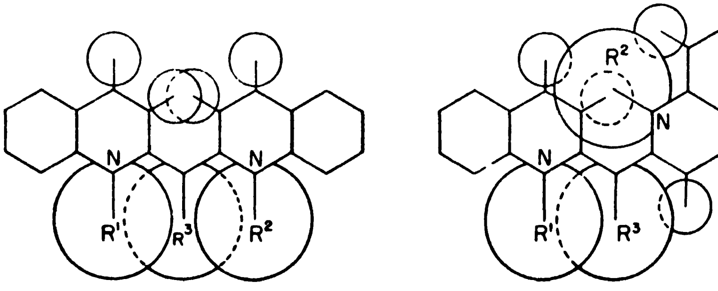
In these dyes the alkyl groups attached to the nitrogens do not lie in a crowded area, even in XVI, and accordingly it is found that in neither dye does replacement of the *N*,*N′*-dimethyl groups by ethyl have an appreciable effect on λ_{max}. There seems to be a tendency for the values of ϵ_{max} to be somewhat higher for the diethyl than for the dimethyl dyes, but determinations of intensity are more subject to experimental error than those of wave length.

Another way of introducing a crowding effect into the molecule of a simple cyanine such as XI is by replacing the hydrogen of the —CH= group of the bridge by alkyl, as in XVII. The drawings show that severe crowding must result, even when the group introduced at the center of the molecule is methyl. The effect on the absorption is extraordinary. Absorption data for different values of R¹, R², and R³ in formula XVII are given in table 1.

TABLE 1

Absorption data for dyes XI and XVII

R¹	R²	R³	λ max. (IN METHYL ALCOHOL)	ε × 10⁻⁴ (IN METHYL ALCOHOL)
In XVII				
			A.	
CH_3	H	CH_3	5200	7.2
CH_3	H	C_2H_5	5225	7.0
C_2H_5	H	C_2H_5	5235	7.6
CH_3	CH_3	CH_3	5745	3.5
CH_3	CH_3	C_2H_5	5770	2.7
C_2H_5	CH_3	C_2H_5	5840	2.1
CH_3	C_2H_5	CH_3	5760	3.1
CH_3	C_2H_5	C_2H_5	5830	2.6
C_2H_5	C_2H_5	C_2H_5	5910	2.0
CH_3	n-C_3H_7	CH_3	5750	3.2
CH_3	n-C_3H_7	C_2H_5	5830	2.7
C_2H_5	n-C_3H_7	C_2H_5	5900	2.1



a

b

XVII

The *N*,*N′*-dimethyl dye has its absorption maximum in alcohol shifted by no less than 545 A. on introduction of the third methyl group at the center, while ϵ_{max} is approximately halved. The substitution in fact converts a pinkish-orange dye into one that is reddish-violet, a change of a magnitude that had not previously been encountered when the first observation of this kind was made several years prior to the publication of Brunings and Corwin's paper.

As has already been noted, the alcoholic absorption of XI is practically unaffected by increase in size of the *N*-alkyl groups, but the absorption of the trimethyl dye is, in general, more sensitive to increase in size of any of the three alkyl groups. However, it is the first change of chain hydrogen to chain methyl which produces by far the greatest effect. Thereafter, increase in size of the alkyl groups from methyl to ethyl produces shifts that, on the whole, are much less although appreciable. Increase in size of the central group from ethyl to *n*-propyl is virtually without effect, on either λ_{max} or ϵ_{max}.

The absorption maxima of the dyes in table 1 (excepting the three dyes with R^3 = *n*-propyl) are plotted in figure 1. The general tendency toward increase in λ_{max} and decrease in ϵ_{max} with increasing crowding of the molecule can be seen very plainly.

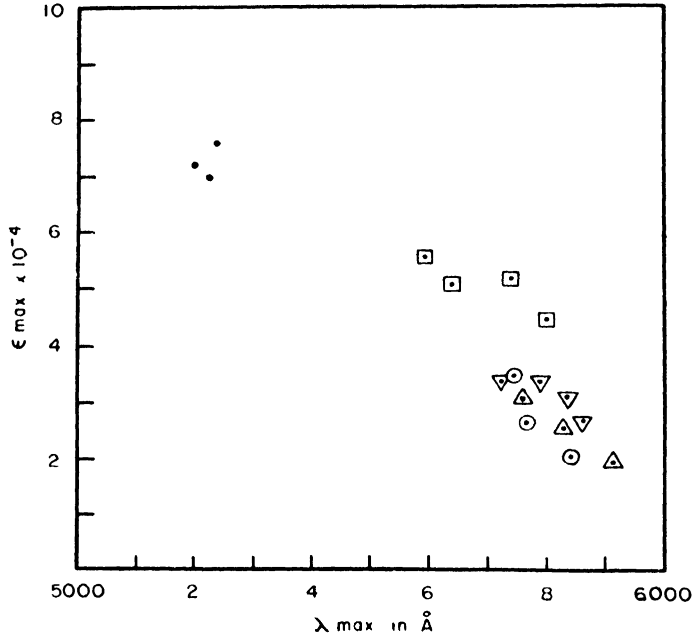


FIG. 1. Plot of λ_{max} against ϵ_{max} for dyes XI, XVII, XVIII, and XIX. ●, dyes XVII with R^3 = H (dyes XI); ⊙, dyes XVII with $R^3 = CH_3$; △, dyes XVII with $R^3 = C_2H_5$; ▽, dyes XVIII; ⊡, dyes XIX.

These dyes apparently follow the Brunings-Corwin pattern in a straightforward manner, yet we cannot be certain that the shifts are wholly due to crowding from planarity. The dyes XVII, aside from being crowded, have a substituent in the chain between the nuclei, and it is barely possible that this might, for some reason not connected with its size, exert a bathochromic effect similar to that of the ethylene group in XX. Nevertheless, the low values of ϵ_{max} of these dyes indicate much distortion from planarity, and it is therefore likely that most of the bathochromic shift shown by these dyes is attributable to the same cause.

It is certain, at any rate, that the shifts which result from *increasing* the size of the alkyl group in the already crowded trimethyl dye XVII (R^1 = R^2 =

R^3 = CH_3) must be ascribed almost wholly to increased distortion from planarity.

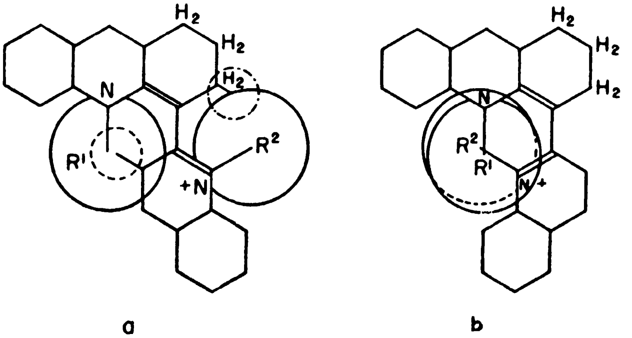
It is interesting to speculate just how great a shift in λ and how great a reduction in ε could be achieved through the distortion from planarity of a given model molecule. We are not yet in a position to answer these questions fully. Difficulties of synthesis must be reckoned with, and although we are not yet certain, our observations appear to indicate that there are limits to the size of crowding substituents, on the favorable side of which dye condensations take place with fair yields of product, but beyond which the condensations fail suddenly and completely. At any rate it is worthy of note that by introducing a central ethyl group into the *N*,*N'*-diethyl dye XI, λ_{max} is shifted by no less than 675 A., from 5235 to 5910 A., while ϵ_{max} is reduced to almost a quarter of its original value, from 7.6 × 10^4 to 2 × 10^4.

TABLE 2

Absorption data for dyes XVIII, XIX, and XX

R^1	R^2	λ max. (IN METHYL ALCOHOL)	ε × 10^{-4} (IN METHYL ALCOHOL)
In XVIII			
		A.	
CH_3	CH_3	5725	3.4
C_2H_5	CH_3	5835	3.1
CH_3	C_2H_5	5790	3.3
C_2H_5	C_2H_5	5860	2.7
In XIX			
CH_3	CH_3	5595	5.6
C_2H_5	CH_3	5740	5.2
CH_3	C_2H_5	5640	5.1
C_2H_5	C_2H_5	5800	4.5
In XX			
CH_3	CH_3	6380	15.2
C_2H_5	C_2H_5	6410	19.0

Up to the present, the dyes dealt with have all been structurally symmetrical, it being possible to write two identical extreme low-energy structures for any of

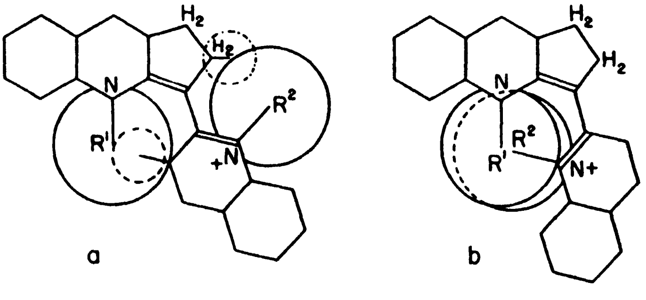


XVIII

them. In the dyes XVIII, which contain a tetrahydroacridine ring linked to one of ordinary quinoline, this strict structural symmetry is no longer present. Nevertheless, the dyes XVIII resemble XVII in that they are both quinoline 2,2′-cyanines with a central alkyl substituent, but in XVIII this alkyl group is bent back to join up to one of the quinoline rings in the 3-position. Owing to this, it is not possible to devise an extended structure for XVIII analogous to XVIIa, and the only planar projections to choose between are XVIIIa and XVIIIb. Of these XVIIIa is the less crowded, and therefore the more plausible, and the choice is confirmed by the following results. If XVIIIa is correct, there should be sensitivity to change in the size of R^1 but much less to that of R^2. (The hydrogen atoms indicated with alternate dots and dashes are those of a $>CH_2$ group and are not in the plane of the quinoline rings. However, they will probably crowd R^2 to some extent.) On the other hand, if XVIIIb is the projection which most nearly represents the molecule, there should be equal sensitivity to R^1 and R^2, since increase in size of either will increase the crowding. The data in table 2 show that λ_{max} is roughly twice as sensitive to change in size of R^1 as to change in size of R^2, pointing to XVIIIa rather than XVIIIb.

There is only one linkage in XVIII about which rotation can occur,—namely, that between the rings. It would seem reasonable to expect that the single-bond character of this linkage would thereby be increased, thus, in turn, increasing the concentration of positive charge on the quinoline nitrogen, rather than that of the tetrahydroacridine ring. An asymmetry could thus be created which does not exist, for instance, in XVII. Such an asymmetry should, if sufficiently great, give rise to a deviation in λ_{max}, but in all probability there is no significant deviation in the present case, for when the absorption maxima of the dyes XVIII are plotted in figure 1, they fall quite close to those given by dyes XVII, where R^3 has a value somewhere between CH_3 and C_2H_5.

The set of four dyes XIX was also prepared from 2,3-trimethylenequinoline. These are similar in structure to XVIII, but the replacement of a six- by a five-membered ring reduces crowding in the neighborhood of both R^1 and R^2. Here



XIX

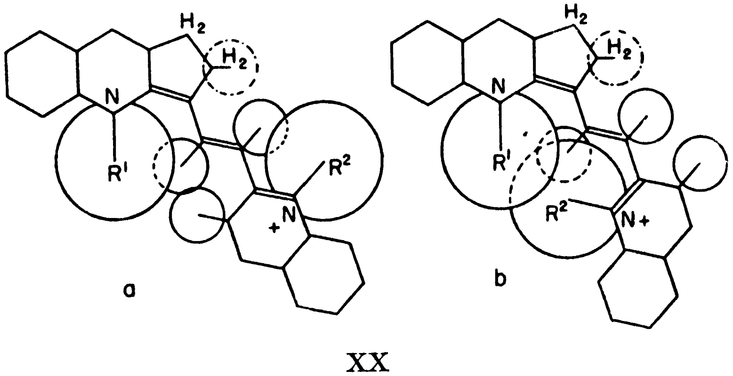
again the data show (table 2) that there is decidedly greater sensitivity to change in size of R^1 than of R^2, thus favoring XIXa over XIXb.

It is at first sight surprising that the shift when R^1 is changed from CH_3 to C_2H_5 is actually greater in XIX than in XVIII, since the latter is the more crowded model. The following explanation for this is suggested: In the dyes XVII, substitution of hydrogen by CH_3 at R^3 causes a very large shift in λ and a drop in ϵ, but beyond this point, further increases in size of R^1, R^2, and R^3 produce considerably smaller effects. It is as if the greater part of the total imaginable distortion for this particular molecular model, and its consequent optical effect, were already realized when $R^1 = R^2 = R^3 = CH_3$. If one now pictures a somewhat similar model but in which the R^1 and R^2 groups are not as close together as in XVII, then substitution of CH_3 for hydrogen at R^3 would produce less distortion and use up a smaller amount of the total realizable shift for this model, so that a *further* increase in size of one of the R groups could have a relatively *greater* effect than in XVII itself.

It is suggested that XVIIIa and XIXa (both with $R^1 = R^2 = CH_3$) are analogous to the two models just discussed at the stage where $R^3 = CH_3$. Distortion will be greater in XVIIIa than XIXa, and the former will be nearer to the position of maximum realizable distortion and be less sensitive to further crowding. Increase in size of the R^1 group thus has a smaller effect than in XIXa.

The positions occupied by the absorption maxima of dyes XIX in figure 1 are in agreement with this interpretation. Alternatively, these points are about what would be expected if it were possible to introduce a group somewhat smaller than methyl, but of similar electronic influence, into the R^3 position of XVII.

Whereas for a dye XIX the choice of structures lies between one that is crowded (XIXa) and one that is more crowded (XIXb), the choice being decided in favor of the former, for the next higher vinylogs the choice is between a structure that is not crowded (XXa) and one that is (XXb), not to include others, not shown, that are even more crowded. The crowding in XXa is so slight that the molecule could undoubtedly become coplanar by adjustment of bond angles alone, and there should be no sensitivity to change in size of R^1 or R^2, such as exists in XIX. On the other hand, XXb requires sensitivity to both R^1 and R^2.

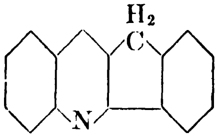


XX

In actual fact, the *N*,*N*-dimethyl and diethyl dyes absorb with values of λ_{max} that are very close (table 2), so that there is definite experimental evidence in favor of XXa.

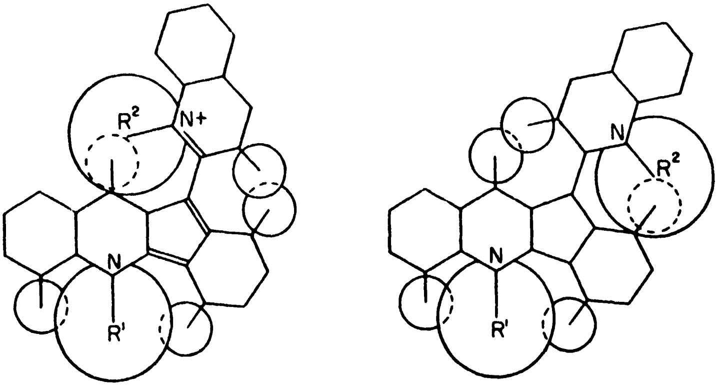
Dye XX has already been referred to as being considered derivable from the carbocyanine XIII by joining carbon atom 3 of one of the quinoline rings to the first carbon of the bridge through an ethylene (—CH_2CH_2—) group, and without loss of planarity. But the most favored arrangement of the rings is not the same for the two dyes, and perhaps this is part of the reason why the dyes XX absorb at markedly longer wave lengths than the dyes XIII.

In the following section, another comparison is made between a short-chain cyanine which is crowded, and its higher vinylog which is not. The dyes are again unsymmetrical, one nucleus being derived from 11-indeno[1,2-*b*]quinoline and the second from quinoline itself.



11-Indeno[1,2-*b*]quinoline

There are only two ways of drawing the short-chain cyanine, XXIa and XXIb, and it can be seen that the R^2 group is crowded against a hydrogen of the indenoquinoline ring to exactly the same extent in one drawing as in the other. The R^1 group, on the other hand, is not crowded; consequently the absorption of the dye should be sensitive to change in size of R^2 but not R^1. The data in table 3 show that this is indeed true. Changing R^1 from methyl to ethyl is almost without effect on λ_{max}, but the same change in R^2 shifts λ_{max} 90 A. in one case and 80 A. in another. The values of ϵ_{max} of all the four dyes examined, however, stay at much the same level.



a b

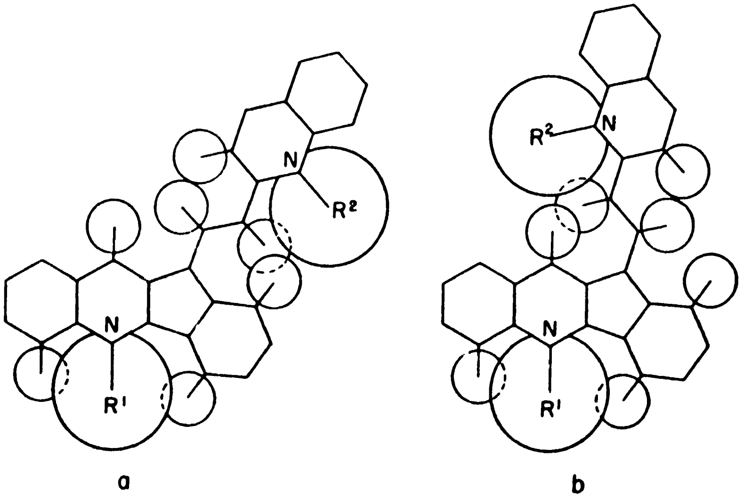
XXI

For the higher vinylog of XXI, structures XXIIa and XXIIb are the most plausible in that they show the least crowding, and in this respect they are equivalent. (The nitrogen atoms at the ends of the chromophoric chain are not the same distance apart in the two structures, however, and it is not known at present how this affects the absorption. It seems reasonable to suppose that the farther the nitrogens are apart, and the higher the dipole moment of the transition, the higher will be the intensity of absorption.)

TABLE 3

Absorption data for dyes XXI and XXII

R^1	R^2	λ max. (IN METHYL ALCOHOL)	ϵ max. $\times 10^{-4}$ (IN METHYL ALCOHOL)
In XXI			
		A.	
CH_3	CH_3	5400	2.5
C_2H_5	CH_3	5420	2.3
CH_3	C_2H_5	5490	2.4
C_2H_5	C_2H_5	5500	2.4
In XXII			
CH_3	CH_3	5520	5.9
CH_3	C_2H_5	5540	6.2



a b

XXII

Neither XXIIa nor XXIIb shows serious crowding, and it seems that such as there is could be completely relieved by adjustment of bond angles. The drawings would not lead to the prediction of sensitivity of the absorption to change in size of R^2 in this case, and the data show this to be true. The absorptions of the dyes where R^2 equals methyl and ethyl differ by only 20 A.

Another interesting relationship is the close similarity of the alcoholic absorptions of the dyes XXI and XXII, where R^2 = ethyl, in spite of the difference in length of the conjugated chains. The values of λ_{max} are very close (see table 3) and it is impossible to distinguish visually between the two purplish-blue solutions. At least two factors contribute to this situation, a crowding effect and a deviation effect. The dye with the shorter chain (XXI) is deeper because of the Brunings–Corwin effect than it would be without the crowding from planarity. But the dye of longer chain-length (XXII) is not crowded; hence it will not be deepened in color for this reason.

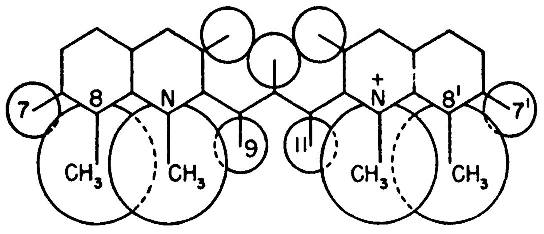
On the other hand, the dyes are rather highly unsymmetrical, with the indenoquinoline ring predictable as the more basic of the two, using the method employed before (2). A shift of λ_{max} to *shorter* wave lengths, or "deviation," could very well result, and this would be much more pronounced for the dye with *longer* chain-length (3). The combination of these two effects could very well produce the result observed.

It is noteworthy that in spite of the planarity of the dyes XXII, they have relatively low values of ϵ_{max}. This may be the result of energetic asymmetry of the extreme structures, unsymmetrical dyes frequently behaving in this way, but this subject will not be pursued further at the present time. The difference in basicity between the nuclei is, however, probably insufficient to warrant inclusion of the dyes of shorter chain-length (XXI) among the *highly* unsymmetrical (and strongly deviating) crowded dyes described in the next section.

Since the crowding in XXI can be relieved by rotation of the nuclei about the linkage between them, this linkage should be inclined toward single-bond character. But this will induce the positive charge of the dye ion in the quinoline nitrogen, and thus increase the basicity of this ring at the expense of the indenoquinoline ring. Any tendency which XXI would have towards a deviation will therefore be expected to be reduced by this effect. Plausible as it is, however, this argument must be used with caution in view of the results obtained with certain of the styryl dyes to be described later.

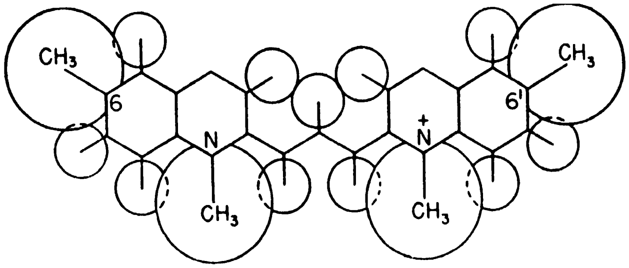
If concentrated alcoholic solutions of XXI and XXII are well diluted with water, the purplish-blue solution of XXII becomes distinctly reddish, doubtless owing to the formation of a polymeric aggregate or aggregates such as is given under similar conditions by the dye pinacyanol (XIII, R = C_2H_5) (11). The solution of XXI, on the other hand, is relatively unchanged by the water and apparently does not aggregate with anything approaching the same ease as XXII, thus following the general behavior of dyes distorted from planarity. By choosing an aqueous solvent it is thus possible to obtain a solution of the dye of *longer* chain-length (XXII) that absorbs at *shorter* wave lengths than its lower vinylene homolog, an unusual relationship even under these narrowly specified conditions.

So far the crowding that has been described is such as will tend to twist the two nuclei of a cyanine dye out of a common plane. An example of crowding of a different kind is provided by XXIII. In this dye the two methyl groups of each



XXIII

$\lambda_{\max}$ = 6095 A. in methyl alcohol
$\epsilon_{\max}$ = 15.7 × 10^4 in methyl alcohol

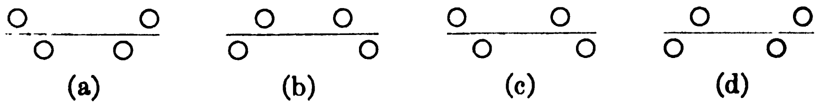


XXIV

$\lambda_{\max}$ = 6085 A. in methyl alcohol
$\epsilon_{\max}$ = 14.3 × 10^4 in methyl alcohol

quinoline ring crowd one another, but not in such a way as seriously to distort the conjugated chain between the nitrogens from planarity. It is thus not surprising that the alcoholic absorption of XXIII is about the same as that of the isomeric XXIV, in which the molecule can be planar.

It seems plausible that the two methyls on each ring in XXIII, prevented to some extent from repelling each other in the plane of the molecule by hydrogen atoms 7 and 9 and 7′ and 11, will crowd each other so that one is thrust somewhat above and the other below the plane of the quinoline rings, thus increasing the average thickness of the molecule. More than this, it may be shown that distortion of the type suggested could give rise to several distinct molecular species, indicated by the following drawings, which are simplified plans of the molecules. The lines represent the length of the molecule in a plane and the


(a) (b) (c) (d)

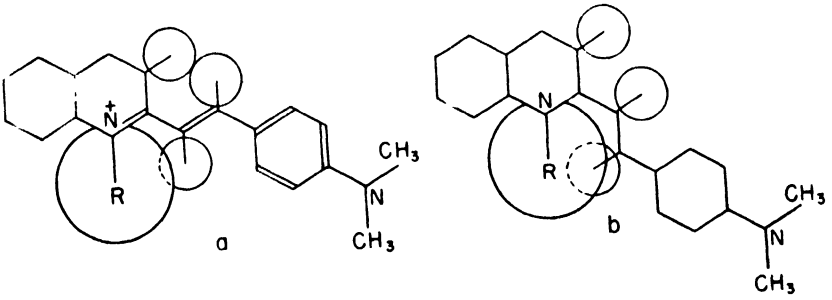
four circles in each drawing the disposition of the methyl groups. Of the four possible arrangements, (a) and (b) are identical, so that there are three possible species with one, (a) + (b), having twice the probability of the other two. Use of models shows that the disposition of the methyl groups in these different species is unfavorable to a close approach of the planar surfaces desirable for aggregate formation.

Whatever the nature of the actual distortion, it is a fact that this dye gives much less of the red aggregate in aqueous solutions than does the isomeric XXIV. Similar behavior is shown by other 2,2′-carbocyanines with substituents (e.g., Cl) in positions 8 and 8′, but not in positions 5 and 5′, 6 and 6′, and 7 and 7′.

VI. CROWDING EFFECTS IN HIGHLY UNSYMMETRICAL DYES OF THE *p*-DIMETHYLAMINOSTYRYL SERIES

Up to this point, the dyes discussed have been either symmetrical or nearly symmetrical cyanines. With these, where the appropriate comparison can be made, distortion from planarity of the resonating system responsible for absorption in the visible invariably produces a shift of λ_{max} to longer wave lengths, although the amount of the shift is not always predictable. There is always a drop in ϵ_{max} also.

The results now to be described for highly unsymmetrical dyes, such as 2-*p*-dimethylaminostyryl-3-methylquinoline methiodide (XXVI), differ significantly from those obtained with the symmetrical cyanines. Dye XXVI is related to the styryl XXV for which structure XXVa is substantially uncrowded and is therefore selected as more probable than XXVb.



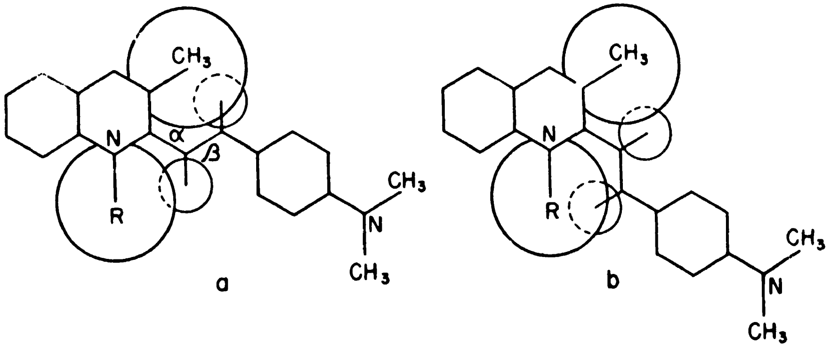
XXV

$$R = CH_3 \begin{cases} \lambda_{max} = 5250 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 6 \times 10^4 \text{ in methyl alcohol} \end{cases}$$

$$R = C_2H_5 \begin{cases} \lambda_{max} = 5250 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 5.8 \times 10^4 \text{ in methyl alcohol} \end{cases}$$

The lack of sensitivity to change of R from methyl to ethyl is in agreement with this choice of XXVa over XXVb. The dyes XXVI absorb at markedly *shorter* wave lengths than XXV, although with strongly reduced values of ϵ_{max}, both effects being more pronounced where R = ethyl.

An explanation which at first seemed satisfactory is as follows: Structures XXVIa and XXVIb are crowded to about the same extent and are therefore about equally probable. But both of them show a hydrogen atom of the vinylene



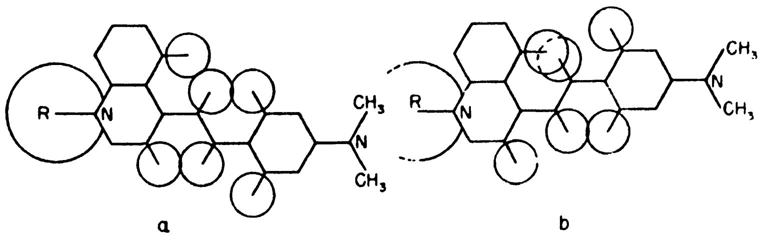
XXVI

$$R = CH_3 \begin{cases} \lambda_{max} = 5000 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 2.7 \times 10^4 \text{ in methyl alcohol} \end{cases}$$

$$R = C_2H_5 \begin{cases} \lambda_{max} = 4930 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 2.2 \times 10^4 \text{ in methyl alcohol} \end{cases}$$

chain crowding an alkyl group,—the 3-methyl group in XXVIa and the *N*-alkyl group in XXVIb. This crowding may be relieved by rotation about the linkages marked α and β, but use of a model shows that greater relief is obtained by rotation about α than about β. This will result in an increase of the single-bond character of α. However, this linkage is already predominantly of single-bond character, since it is a single bond in the extreme structure of lower energy, i.e., that in which the benzene ring of the styryl group is benzenoid. (The arrangement of the linkages of the conjugated chain in this structure follows that shown in XXVa.) Thus, the effect of crowding in XXVI is further to increase the stability of that structure which is already the more stable. The asymmetry of the extreme structures is therefore increased over that prevailing in XXV, resulting in an increase in deviation over that of XXV, which, in turn, could easily result in a net shift of λ_{max} to shorter wave lengths. Also, the effect would be greater, the greater the size of R.

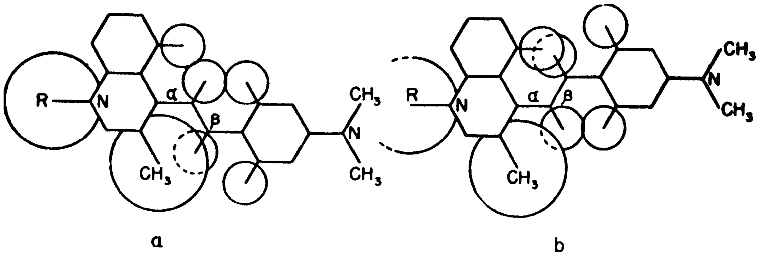
The plausibility of this explanation was apparently confirmed by the fact that very similar results were obtained on comparing 4-*p*-dimethylaminostyryl-3-methylquinoline methiodide (XXVIII) with the corresponding dye lacking the 3-methyl group (XXVII). The drawings show XXVII to be uncrowded in XXVIIa and XXVIII to be about equally crowded in XXVIIIa and XXVIIIb.



XXVII

$$\begin{cases} \lambda_{max} = 5440 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 4.5 \times 10^4 \text{ in methyl alcohol} \end{cases}$$

$$R = C_2H_5 \begin{cases} \lambda_{max} = 5460 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 4.6 \times 10^4 \text{ in methyl alcohol} \end{cases}$$



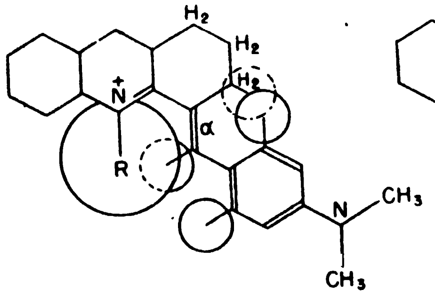
XXVIII

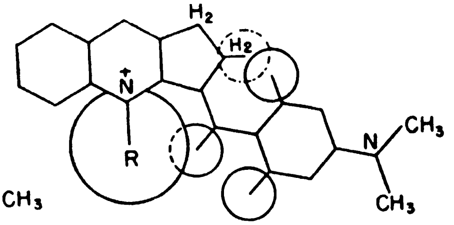
$$R = CH_3 \begin{cases} \lambda_{max} = 5100 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 2.3 \times 10^4 \text{ in methyl alcohol} \end{cases}$$

$$R = C_2H_5 \begin{cases} \lambda_{max} = 5115 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 2.4 \times 10^4 \text{ in methyl alcohol} \end{cases}$$

Here also the crowded dyes XXVIII absorb at *shorter* wave lengths, and with lower values of ϵ_{max}, than the related uncrowded dyes XXVII, and a precisely similar explanation may be offered to that advanced for XXV and XXVI. The crowding can better be relieved by rotation about the linkage α than about β and this will still further increase the single-bond character of α and hence the deviation of the dye, so that absorption at shorter wave lengths than XXVII is not surprising. In these dyes, however, the R groups in the quinoline nitrogen do not enter into any crowding; hence neither XXVII nor XXVIII is sensitive to increase in size of R, as the data show.

This argument, however, is not satisfactory in treating the absorptions of the styryl, or rather benzylidene, dyes XXIX and XXX. In XXIX, for which only the structure shown need be considered, there is crowding between the R





XXIX

$$R = CH_3 \begin{cases} \lambda_{max} = 5070 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 2.8 \times 10^4 \text{ in methyl alcohol} \end{cases}$$

XXX

$$R = CH_3 \begin{cases} \lambda_{max} = 5380 \text{ A. in methyl alcohol} \\ \epsilon_{max} = 4.7 \times 10^4 \text{ in methyl alcohol} \end{cases}$$

$$R = C_2H_5\left\{\begin{array}{l}\lambda_{\max} = 5010 \text{ A. in methyl alcohol}\\ \epsilon_{\max} = 2.1 \times 10^4 \text{ in methyl alcohol}\end{array}\right. \qquad R = C_2H_5\left\{\begin{array}{l}\lambda_{\max} = 5400 \text{ A. in methyl alcohol}\\ \epsilon_{\max} = 4.8 \times 10^4 \text{ in methyl alcohol}\end{array}\right.$$

group and the hydrogen of the chain. This can clearly be remedied by rotation about linkage α, which, according to the previous argument, would increase the single-bond character of this linkage. But α is a double bond in the low-energy extreme structure, the linkages of which are those shown, consequently the crowding in this particular dye would be expected to favor the higher-energy extreme structure rather than the lower, and thus *decrease* the deviation and exert a bathochromic influence. Since the effect should be stronger the larger the group R, the *N*-ethyl derivative of XXIX by this reasoning should absorb at longer wave lengths than the *N*-methyl dye, whereas in actual fact the reverse is true. Furthermore, the dyes XXIX should by this reasoning absorb at longer wave lengths than the very similarly constituted dyes XXX but in which crowding is virtually absent. Again, the reverse actually holds.

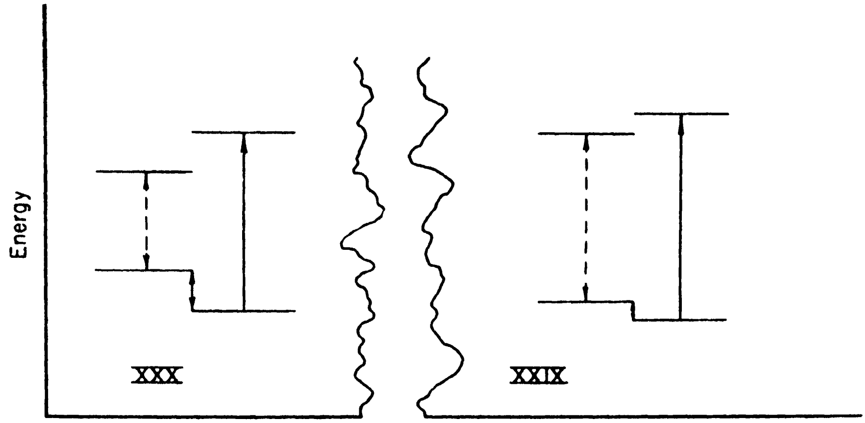


FIG. 2. Lowered resonance energy (←→) in XXIX relative to XXX gives greater separation of the levels of the extreme structures (←--→) and hence of the ground and excited states (—→).

Because of these results the argument previously advanced must either be abandoned or given secondary significance, and for the present the best explanation of the facts seems to be that crowding in highly unsymmetrical dyes reduces the resonance interaction, thus increasing the separation of the levels of the structures, and hence of the levels of the ground and excited states, as shown in figure 2. Although it is shown lower in the diagram, it is not intended to imply that the low-energy extreme structure is actually lower in XXIX than in XXX, merely that the *separations* are greater in XXIX.

Since with symmetrical and nearly symmetrical cyanines of short chain-length the effect of crowding is to shift λ to longer wave lengths and with highly unsymmetrical dyes the effect is to shift λ to shorter wave lengths, it would seem as if dyes of an intermediate classification must be capable of existence, which would show virtually no shift of λ but only a drop in ϵ_{max} as a result of crowding. So far we have not encountered an example of this type.

VII. PROGRESSIVE INCREASE IN CROWDING IN A CONNECTED SERIES OF DYES

The dye XXXI, containing two pyridine rings linked together by a single =CH— group, is the simplest member of the series XXXI to XXXV, the higher members of which may be regarded as derived from the lower by fusion to the nuclei of benzene residues. The absorption curves of these five dyes in methyl alcohol are shown in figure 3.

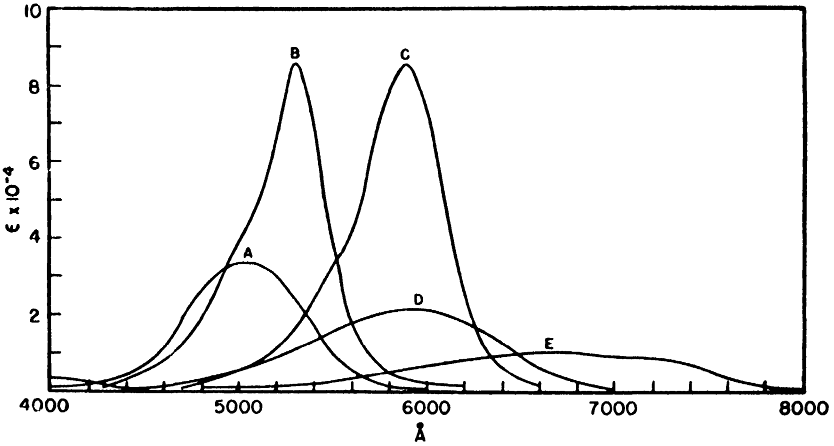
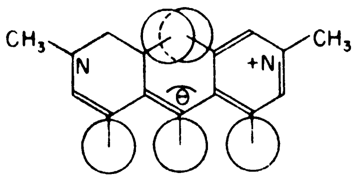
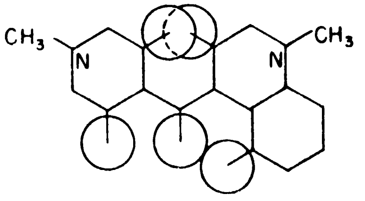


FIG. 3. Absorption spectra in methyl alcohol. A = XXXI; B = XXXII; C = XXXIII; D = XXXIV; E = XXXV.



XXXI

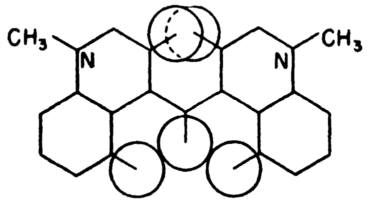
λ_{max} = 5045 A. in methyl alcohol
ϵ_{max} = 3.4×10^4 in methyl alcohol



XXXII

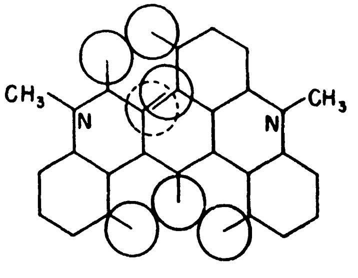
λ_{max} = 5300 A. in methyl alcohol
ϵ_{max} = 8.7×10^4 in methyl alcohol

Only the projection shown is possible for XXXI. The crowding of the hydrogen atoms in the upper part of the figure is like that already encountered (e.g., XI) and can doubtless be accommodated very easily to preserve planarity, especially by increase in the angle θ, particularly as there is room to spare in the lower part of the figure. However, it is noteworthy that the dye does not have a high ϵ_{max} (12).



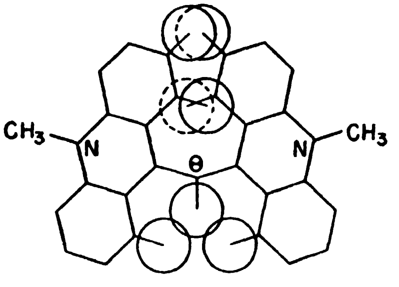
XXXIII

λ_{max} = 5885 A. in methyl alcohol
ϵ_{max} = 8.6 × 10^4 in methyl alcohol



XXXIV

λ_{max} = 5940 A. in methyl alcohol
ϵ_{max} = 2.2 × 10^4 in methyl alcohol



XXXV

λ_{max} = 6710 A. in methyl alcohol
ϵ_{max} = 1.1 × 10^4 in methyl alcohol

Addition of a benzene residue to give XXXII will result in a somewhat tighter packing of the molecule in the lower part of the figure; nevertheless XXXII absorbs with a considerably higher value of ϵ_{max} and with a shift in λ toward the longer waves (12). The additional conjugation introduced as a result of adding the benzene residue is doubtless partly responsible for these effects.

Addition of a second benzene residue gives XXXIII. The molecule is still more tightly packed, and it is possible that there is now a slight distortion from planarity, sufficient to account for the fact that ϵ_{max} is not higher than the value for XXXII, in spite of the extra conjugation in the molecule.

In XXXIV the crowding is so pronounced that planarity cannot be maintained and the drop in ϵ_{max} is now very marked, although the shift in λ is very small. The band, too, is much broader than that of XXXIII. There is a still further drop in ϵ_{max} in XXXV, where the crowding must be extremely severe, and the band is very broad and flat. Solutions of this dye are a rather dull bluish-green. (The figure of XXXV is drawn with angle θ larger than normal in order to avoid confusion in the upper part of the drawing.)

There can be little doubt that a multiplicity of factors enters into the absorptions of these dyes. For one thing, the basicity of the nuclei in the three symmetrical dyes diminishes with increasing complexity, and there is reason to believe that, other things being equal, greater depth of color is shown in a symmetrical cyanine the more basic the nucleus. This factor will thus tend to make XXXI relatively deeper in color with respect to XXXIII than it would be otherwise, and XXXIII relatively deeper with respect to XXXV. However, the Brunings–Corwin effect, operating strongly in XXXV, will make this dye much deeper in color than it would be otherwise, and will probably much more than offset the lightening effect due to the weak basicity of the acridine nucleus.

Again, dyes XXXII and XXXIV are unsymmetrical cyanines, and might be expected to show deviations. It is indeed true that these dyes absorb with λ_{max} well on the short-wave-length side of the average of the values of the related symmetrical dyes, although it is doubtful if the deviation of 165 A. shown by XXXII (the mean of 5045 and 5885 A. is 5465 A., so that the deviation is 5465 − 5300 = 165 A.) is a result solely of the unequal basicities of the nuclei. It is possible that XXXIII is somewhat deeper in color than it would be otherwise, because of the operation of the Brunings–Corwin effect, thus increasing the apparent deviation of XXXII.

The considerable deviation of 360 A. shown by XXXIV is likewise probably due in part to the difference of basicity of the nuclei composing the dye, in part to the absorption of the parent dye XXXV at very much longer wave lengths owing to the Brunings–Corwin effect. Incidentally, it is worth pointing out that with λ_{max} = 6710 A., the acridine dye XXXV is by far the deepest-colored simple (monomethine) cyanine yet described.

VIII. CONCLUSIONS

The foregoing constitutes a preliminary survey of a field that is at present by no means completely explored, and is still incompletely understood. Nevertheless, it is possible to trace certain generalities.

To the single example of a crowded symmetrical cyanine provided by Brunings and Corwin (4) many others have now been added. In almost all cases the absorption maximum is shifted to longer wave lengths as a result of crowding the two nuclei of a cyanine out of a common plane, or increasing the crowding in an already distorted molecule. (The single exception is XIV, R = C_2H_5, considered relative to the already crowded XIV, R = CH_3.) The extent of the shift, however, for a comparable amount of crowding varies from type to type. Somewhat unsymmetrical dyes behave similarly on introduction of a crowding group, but where an uncrowded dye is sufficiently unsymmetrical to show a large deviation in λ_{max}, then crowding the conjugated system out of planarity shifts the absorption to *shorter* wave lengths. The crowded dyes of both categories, however, behave alike in that they show a marked drop in ϵ_{max} compared to the related uncrowded dyes.

The connection between steric hindrance and planarity and molecular aggregation is touched on very briefly in the present paper. It is hoped to deal with this subject more fully at a later date.

The authors are greatly indebted to Mr. E. E. Richardson and his colleagues for most of the spectral absorptions, to Dr. G. L. Beyer for the absorptions which showed the aggregation in aqueous solutions of dyes XXIII and XXIV, and to Dr. William West for many helpful discussions.

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THE ULTRAVIOLET ABSORPTION SPECTRA OF ANTHRACENE DERIVATIVES[1, 2]

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The effects of various substituents on the ultraviolet absorption spectrum of anthracene are considered. The band shifts observed are correlated with the type and position of the substituent group. It is suggested that the substituent may modify the energies of both the ground and the excited states of the molecule and that the effect on the excited state is probably influenced by the position of the substituent relative to certain axes in the molecule.

I. INTRODUCTION

In an endeavor to interpret the effect of substituents on the spectra of triphenylmethyl ions and other dyes, G. N. Lewis and coworkers (6, 7) took account of the orientation of the molecule in the electric field and designated the absorption bands as x-bands or y-bands on the assumption that they were associated with electric moments directed along mutually perpendicular axes in the main plane of the molecule. A similar hypothesis had been applied previously by Scheibe (13, 14) to account for the abnormal spectra of certain molecular aggregates.

The importance of such directed excitation in connection with the absorption spectra of hydrocarbons has been recognized by Pauling and Zechmeister (16, 17) and by Mulliken (8), who have described the spectrographic changes which accompany *trans*→*cis* isomerism of carotenoids in terms of the effect of the isomerization on the linear extension of the molecule.

The ultraviolet absorption spectra of hydrocarbons such as anthracene, pyrene, and chrysene (2), which contain several condensed aromatic rings, usually exhibit much more structure than do the spectra of the triphenylmethyl ions or the carotenoids. The introduction of substituents into these complex aromatic hydrocarbons at different positions on the ring systems modifies the spectra in a complex manner. In an earlier publication from this Laboratory (3) four distinct types of substitution effects have been recognized and designated by the symbols C (conjugation), Fs (fine-structure), B (bathochromic), and S (steric).

At the present time, a rigorous treatment of the electronic spectra of such complicated molecules by the methods of quantum mechanics is impractical, and it is therefore of interest to examine whether the concept of an oriented ex-

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citation mechanism can be applied to account for some of the substitution effects observed in these polynuclear aromatic hydrocarbons. Furthermore, from a comparative study of such substitution effects some insight might be gained into the process of light absorption by the parent hydrocarbon molecule.

II. THE ELECTRONIC STRUCTURE OF ANTHRACENE

For the purposes of such a study, anthracene has been selected for special consideration since it possesses several advantageous features. Its ultraviolet absorption spectrum can be be divided into two clearly distinguishable parts, associated with two groups of maxima, designated A–B and C–H in figure 1. It seems reasonable to assume that these two regions of the spectrum are related to separate states of electronic excitation. The several maxima in the C–H band group are almost certainly vibrational sub-levels; their frequency differences (table 1) are constant and probably related to the —C—H bending vibration which occurs in the infrared spectrum near 1450 cm.$^{-1}$ The shape of the anthracene molecule is also favorable for such a study, since the linear extension along each of the three principal axes is appreciably different; at the same time the molecule retains considerable symmetry so that it is reasonable to postulate that if the electric moments associated with the various absorption bands are directed along specific axes, those axes in all probability will correspond with the axes *aa'*, *bb'*, and *cc'* on figure 1.

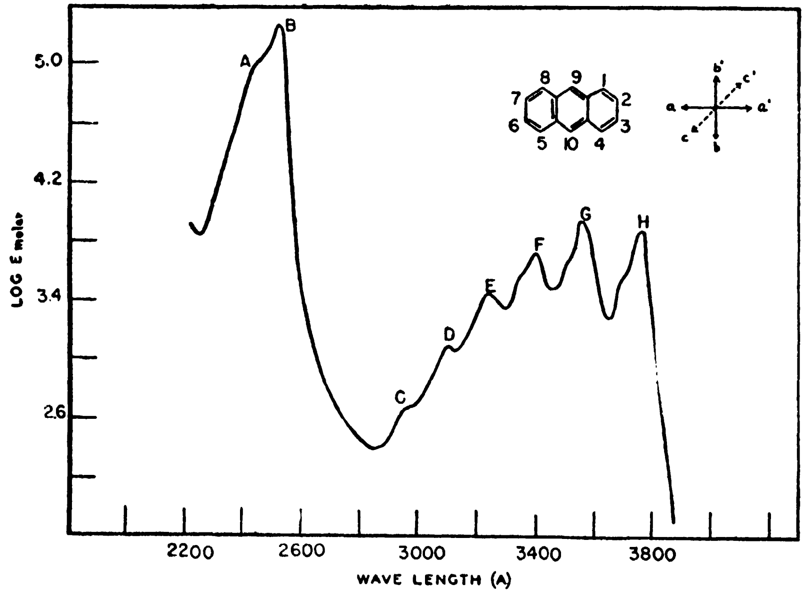
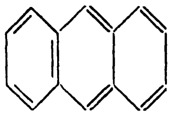
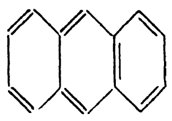


FIG. 1. Ultraviolet absorption spectrum of anthracene (solvent ethanol)

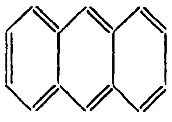
The process of electronic excitation may be visualized in a highly simplified form in the following terms. The four uncharged structures Ia–Id will make



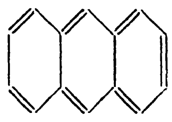
Ia



Ib



Ic



Id

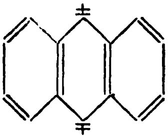
TABLE 1

Position of absorption maxima in ultraviolet absorption spectrum of anthracene

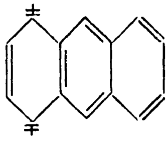
MAXIMUM*	FREQUENCY	FREQUENCY DIFFERENCE
a. Solvent ethanol		
	$cm.^{-1}$	$cm.^{-1}$
B	39,720 ± 40	
D	32,260 ± 30	1370
E	30,890 ± 25	1420
F	29,470 ± 20	1410
G	28,060 ± 20	1420
H	26,640 ± 15	
b. Solvent *n*-heptane		
B	39,680 ± 40	
D	32,360 ± 30	1350
E	31,010 ± 25	1470
F	29,540 ± 25	1410
G	28,130 ± 20	1460
H	26,670 ± 15	

* The maxima A and C are too flat to permit of an accurate determination of the position.

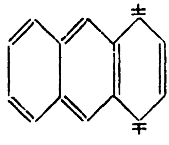
the major contributions to the resonance in the ground state of the molecule, and it will be assumed that other structures such as Ie–Ii, which involve a separation of charge, will be of sufficiently higher energy to render their contributions to the resonance of the ground state of negligible importance. In the electronic-



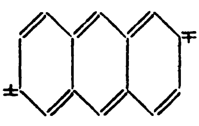
Ie



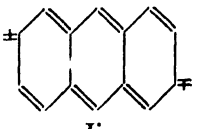
If



Ig



Ih



Ii

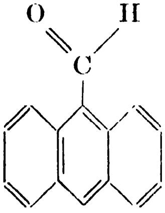
ally excited states, the contributions of such structures may well be significant. These polar structures can be divided into two groups: Ie–Ig, in which the polarization is directed along the *bb'*-axis; and Ih–Ii, in which the polarization is directed somewhat diagonally but closer to the *aa'*-axis. If these structures participate in the resonance of the excited states, it is to be anticipated that the electric moments associated with the process of excitation will be directed along axes simply related to the directions of these polarizations.

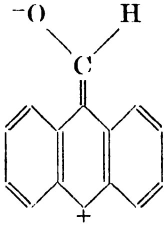
III. SPECTRA OF ANTHRACENE DERIVATIVES

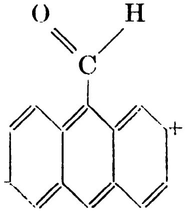
A. Substituents exhibiting conjugation effects

The direct demonstration of such oriented excitation in the unsubstituted hydrocarbon offers considerable experimental difficulty, since it requires the alignment of the absorbing molecule with respect to the electric vector of the exciting radiation, but a simpler indirect approach to the problem can be made through a study of suitably chosen substituted compounds, particularly those which exhibit a predominant C-effect (3).

In 9-anthraldehyde (IIa) the conjugation in the direction of the *bb'*-axis is so altered that in the excited state corresponding to one of the Ie structures the negative charge is transferred from a carbon to an oxygen atom and the resultant structure (IIb) should be more stable. On the other hand, the energies of IIc and the corresponding Ih structure will differ much less, since the charge remains on the carbon atoms in both. We may therefore expect that the introduction of the aldehyde group at the 9-position would cause a larger displacement of an absorption band associated with excitation along the *bb'*-axis than of an absorption band associated with an electric moment oriented in some other direction. The spectra of anthracene and 9-anthraldehyde in ethanol solution are compared in figure 2. Both the A–B and the C–H groups of bands are displaced bathochromically on introduction of the aldehyde group, but the effect is much greater on the C–H group. In column 6 of table 2 the frequency shifts of the absorption maxima resulting from these substitutions are listed; while the B maximum is shifted by 1550 cm.$^{-1}$, the displacements of the E, F, G, and H maxima are 2650, 2590, 2930, and 2890 cm.$^{-1}$, respectively.


IIa


IIb


IIc

In table 2 and figures 3 and 4 similar data are given for 9-cyanoanthracene and 9-nitroanthracene. These are in agreement with the observations on the 9-aldehyde in demonstrating that the introduction of these substituents at the 9-position displaces the C–H group of maxima much more than the A–B.

In figure 5 the spectrum of 2-aminoanthracene (IIIa) is compared with that of the corresponding aminium ion (IV). The spectrum of the ion resembles that of the unsubstituted hydrocarbon, but the spectrum of the free base exhibits several points of difference, the most significant of which, for the purpose of the present study, being the large bathochromic displacement of the A–B band group. The development of the broad absorption band at the extreme long-wavelength end of the spectrum is a feature common to aromatic amines of this general type. A superficial inspection of the curves in figure 5 suggests further that in 2-aminoanthracene the C–H bands may actually be shifted hypsochromically with respect to those of the ion, or of anthracene itself; however, an analysis of the frequency shifts must be treated with some reserve in this case, since some doubt exists as to which of the maxima in the ion spectrum corresponds with a given maximum in the spectrum of the free base. The spectra of anthracene and 2-acetoanthracene shown in figure 6 exhibit similar features, and comparison of the curves of figures 5 and 6 with those of figures 2–4 shows clearly that the substituent at position 9 exerts its main effects on the C–H band group, while the substituent at position 2 principally influences the A–B group.

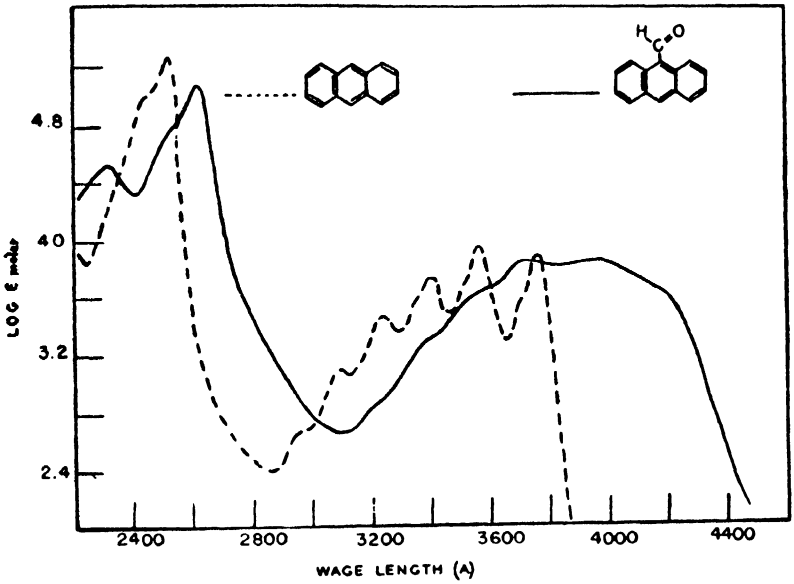
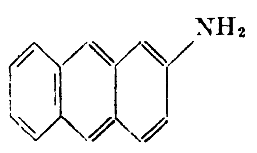
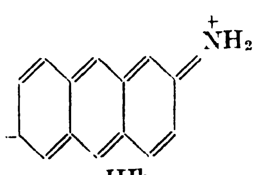


FIG. 2. Ultraviolet absorption spectra of anthracene and 9-anthraldehyde (solvent ethanol).



IIIa



IIIb

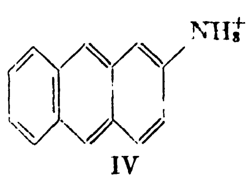


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TABLE 2

Frequency shifts of anthracene absorption maxima on introduction of conjugatable substituents

COMPOUND	SOURCE*	SOLVENT	MAXIMUM†	FREQUENCY‡	SHIFT FROM ANTHRACENE
				cm.$^{-1}$	*cm.*$^{-1}$
9-Anthraldehyde	a	Ethanol	B	38,170	1550
			E	28,170	2720
			F	26,840	2630
			G	25,130	2930
			H	23,750	2890
9-Cyanoanthracene	a	Ethanol	B	39,060	650
			E	28,900	1990
			F	27,510	1960
			G	26,180	1880
			H	24,810	1830
9-Nitroanthracene	i	Ethanol	B	39,680	40
			E	30,210	680
			F	28,820	650
			G	27,550	510
			H	26,180	460
2-Aminoanthracene	d	Ethanol		38,170	
				31,300	
				29,800	
				28,290	
				24,390	
2-Acetoanthracene	g	Ethanol		38,460	
				37,040	
				30,670	
				29,330	
				27,860	
				26,250	
				25,130	
2,3,9,10-Tetraphenylanthracene	b	Ethanol	B	34,480	5240
			E	28,900	1990
			F	27,470	2000
			G	26,110	1950
			H	24,700	1940

* See footnote to table 3.

† See figure 1.

‡ The estimated experimental error in the determination of the frequencies of the maxima varies between 40 cm.$^{-1}$ at the high frequencies and 15 cm.$^{-1}$ at the low frequencies, as shown in table 1.

In 2-aminoanthracene the main effect of the amino group will be to lower the energy of one of the Ih structures, yielding instead IIIb. In view of the closely knit structure of these molecules, it is hardly to be anticipated that they will

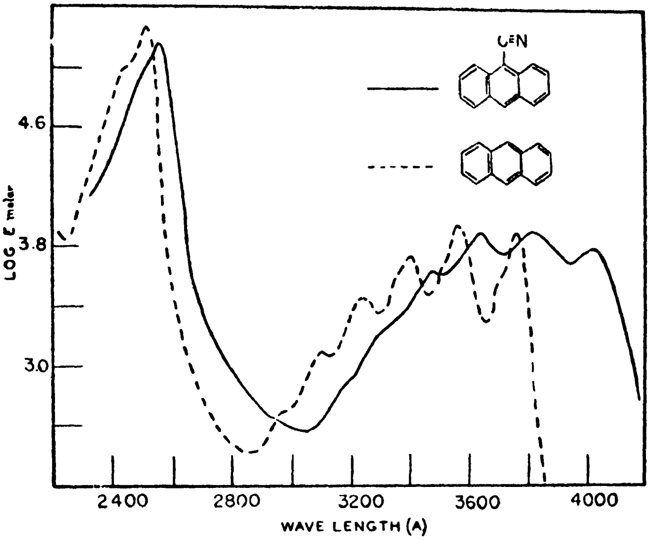


Fig. 3. Ultraviolet absorption spectra of anthracene and 9-cyanoanthracene (solvent ethanol).

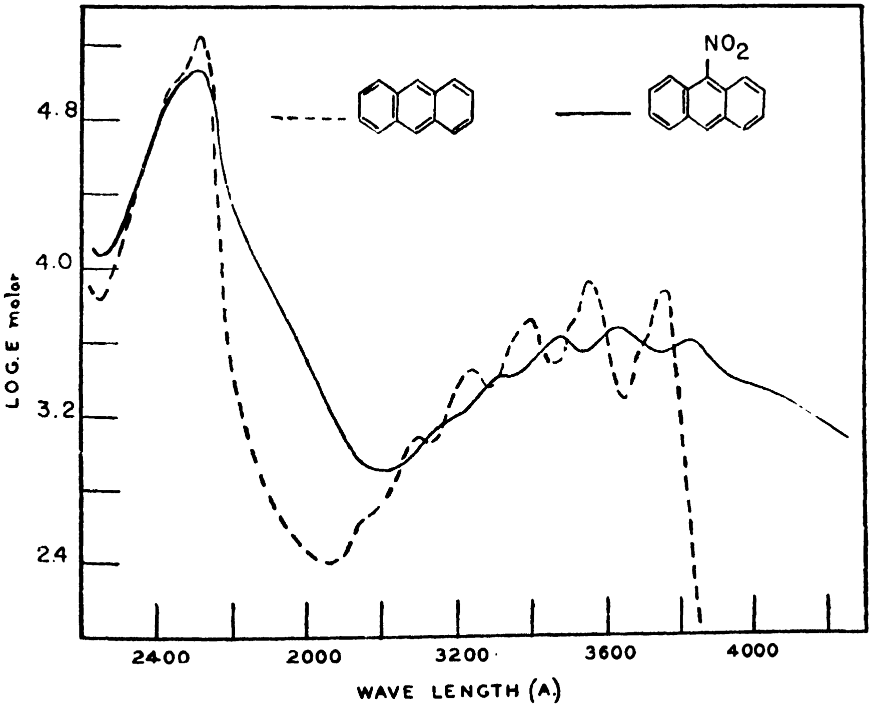


Fig. 4. Ultraviolet absorption spectra of anthracene and 9-nitroanthracene (solvent ethanol).

exhibit such clearly distinctive x-bands and y-bands as do molecules such as carotenoid pigments and triphenylmethyl ions, in which the conjugated systems are more clearly directed along specified axes. Nevertheless, the positional effects of the substituents described above suggest that in anthracene the A–B maxima are associated primarily with excitation directed along the aa'-axis and the C–H maxima with an excitation process directed along the bb'-axis.

B. Substituents exhibiting steric effects

Several investigators (1, 2, 3, 9, 10) have drawn attention to the effects of steric hindrance on the spectra of aromatic compounds. Where the introduction of a substituent increases the energy barriers opposing the establishment of a planar conjugated system, such steric effects become of major importance.

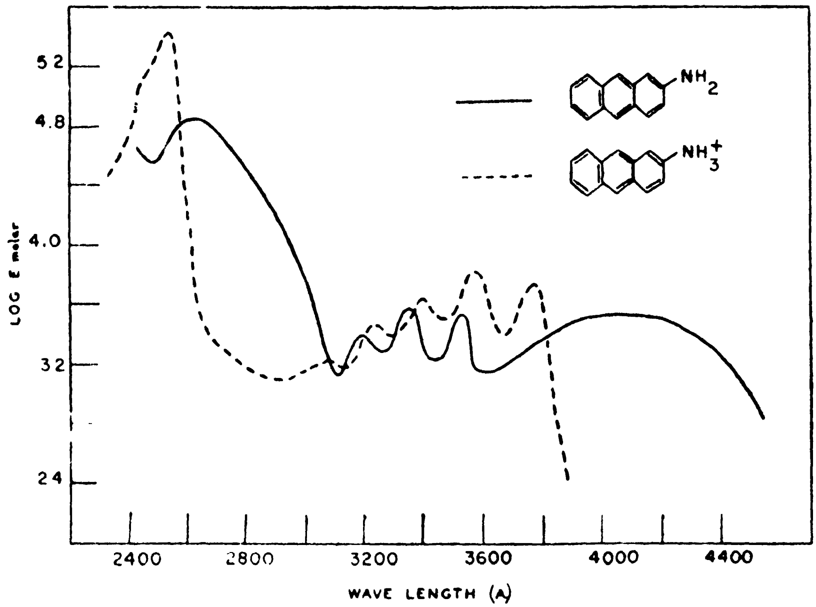


FIG. 5. Ultraviolet absorption spectra of 2-aminoanthracene (solvent ethanol) and 2-aminoanthracene hydrochloride (solvent 2 N hydrochloric acid in 50 per cent aqueous ethanol).

The spectra of certain 9,10-diarylanthracenes are of particular interest in this connection. The introduction of phenyl groups at positions 9 and 10 causes very little change in the anthracene spectrum (3); it is indeed somewhat surprising to observe that the introduction of methyl groups actually produces a greater displacement (*vide infra*). In figure 7 are shown the spectra of 9,10-diphenylanthracene and 2,3,9,10-tetraphenylanthracene (V). Comparison of the data in table 2 indicates that the introduction of the additional phenyl substituents at positions 2 and 3 displaces the C–H maxima by only 800 cm.$^{-1}$, while the B maximum is shifted by 4000 cm.$^{-1}$ Whereas the phenyl groups at

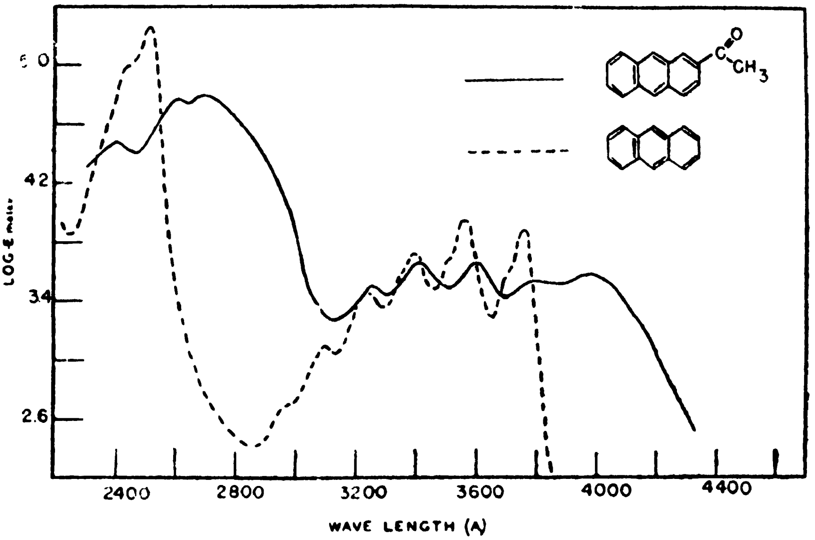


FIG. 6. Ultraviolet absorption spectra of anthracene and 2 acetoanthracene (solvent ethanol).

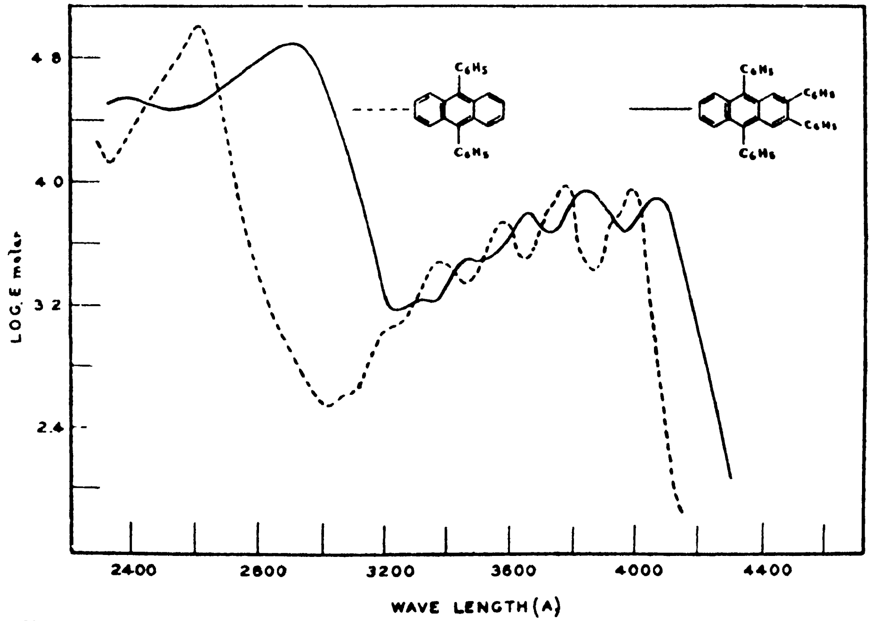
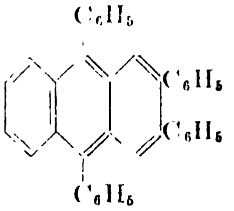


FIG. 7. Ultraviolet absorption spectra of 9,10-diphenylanthracene and 2,3,9,10-tetraphenylanthracene (solvent ethanol).

positions 9 and 10 are hindered to such an extent that they probably lie more or less perpendicular to the main plane of the anthracene molecule, the phenyl groups at positions 2 and 3 are less hindered and, like the other 2-substituents discussed above, exert a major action on the A–B maxima presumed to be associated with an electric moment directed along or near to the *aa'*-axis.

In 9,10-diphenylanthracene, the additive contribution of the meso-phenyl groups to the total absorption of the molecule is too small to be observed, but in 9,10-di(1-naphthyl)anthracene[3] (VI) and 9,10-di(2-naphthyl)anthracene[8] (VII) the naphthyl chromophores absorb strongly near 3200 A. in the region of the anthracene minimum, and in figures 8 and 9 the spectra of these two compounds are shown, together with the computed curves for mixtures of 1 mole of 9,10-dimethylanthracene with 2 moles of 1-methyl- or 2-methyl-naphthalene. The additive contributions of the naphthyl chromophores are clearly in evidence. The methyl derivatives are to be preferred to the unsubstituted hydrocarbons as comparison substances, since they allow a rough correction to be made for



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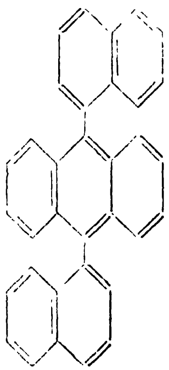

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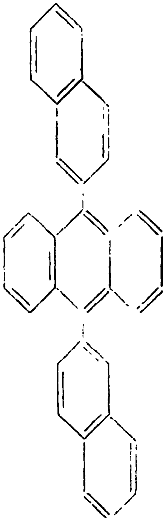
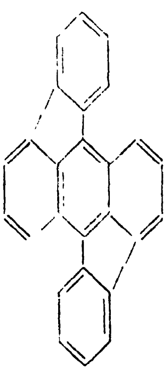


VII



VIII

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[8] Compounds supplied by Dr. R. B. Woodward.

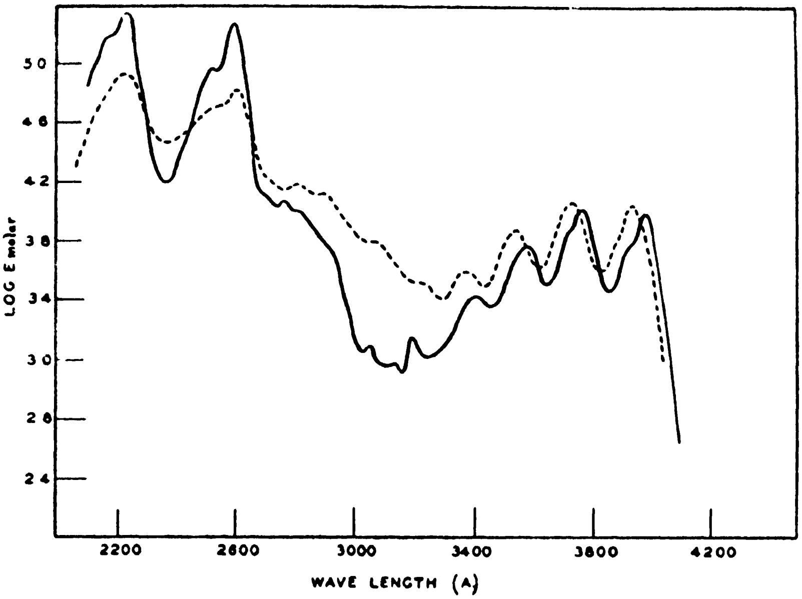

FIG. 8. Ultraviolet absorption spectra: - - - - - - - -, 9,10-di(1-naphthyl)anthracene; ———, computed curve for 1 mole of anthracene and 2 moles of 1-methylnaphthalene (solvent ethanol).

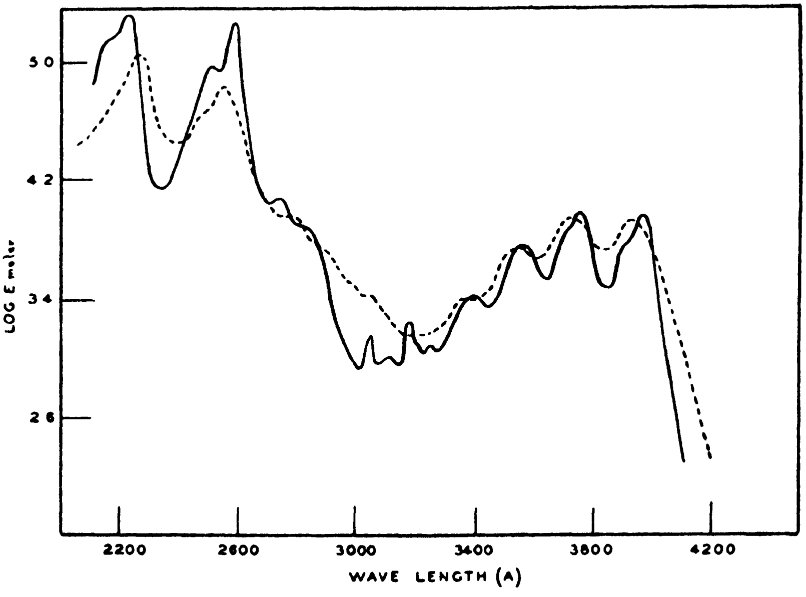

FIG. 9. Ultraviolet absorption spectra: - - - - - - - -, 9,10-di(2-naphthyl)anthracene; —, computed curve for 1 mole anthracene and 2 moles of 2-methylnaphthalene (solvent ethanol).

the bathochromic effect caused by the replacement of the meso —C—H bond by a pseudo-aliphatic C—C bond.

If the steric restrictions on the coplanarity of 9,10-diphenylanthracene could be eliminated, a spectrum very different from that of anthracene might ensue. In rubicene (VIII) this is partly achieved by the introduction of bridge linkages between the phenyl groups and the anthracene ring system. This removes two of the centers of steric interference and replaces them by linkages which force the meso-aryl groups into a condition approaching planarity. The spectra of 9,10-diphenylanthracene and rubicene are shown in figure 10. The curves differ

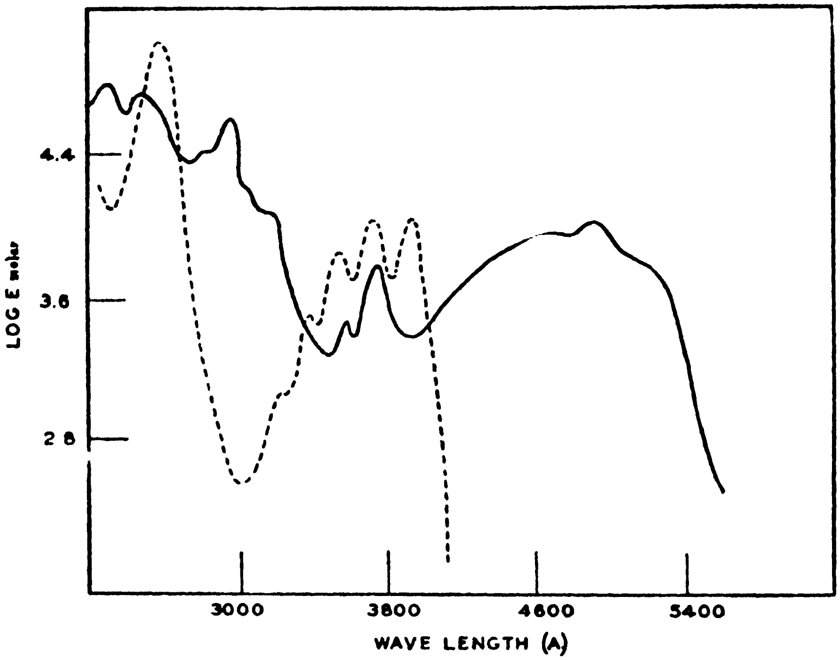

FIG. 10. Ultraviolet absorption spectra: ——, rubicene, - - - - - -, 9,10-diphenylanthracene (solvent ethanol).

quite considerably, the rubicene spectrum extending very much further towards longer wave lengths suggestive of a considerable diminution in the levels of certain of the excited states. The introduction of such bridge linkage, however, probably causes changes of a more fundamental character in the electronic structure, since it permits of the participation in the resonance of new types of structures in which the bridge linkage is ethylenic.

C. *Substituents exhibiting B-effects*

The substituents considered in the above discussions are all of the potentially conjugatable type and, in the absence of steric inhibitions, will facilitate charge transfer in the conjugated systems to which they are attached. This is not so in the case of saturated substituents, such as alkyl groups and aminium ions. It

TABLE 3

Frequency shifts of anthracene absorption maxima on introduction of non-conjugatable substituents

COMPOUND	SOURCE*	SOLVENT	MAXIMUM†	FREQUENCY	SHIFT FROM ANTHRACENE
				cm.⁻¹	*cm.*⁻¹
9-Methylanthracene	a	Ethanol	B	39,180	540
			E	30,120	770
			F	28,710	780
			G	27,320	740
			H	25,890	750
		n-Heptane	B	39,060	620
			E	30,170	840
			F	28,780	760
			G	27,360	770
			H	25,940	730
9,10-Dimethylanthracene	a, c	Ethanol	B	38,460	1260
			E	29,420	1470
			F	27,930	1540
			G	26,530	1530
			H	25,130	1515
		n-Heptane	B	38,460	1220
			E	29,410	1600
			F	28,010	1530
			G	26,560	1570
			H	25,160	1510
9,10-Diphenylanthracene	a	Ethanol	B	38,610	1110
			E	29,670	1220
			F	28,250	1220
			G	26,880	1180
			H	25,510	1130
9-Methyl-10-ethylanthracene	c	*n*-Heptane	B	38,390	1290
			E	29,410	1600
			F	27,970	1570
			G	26,530	1600
			H	25,130	1540
9-Methyl-10-*n*-propylanthracene	c	*n*-Heptane	B	38,390	1290
			E	29,370	1640
			F	27,970	1570
			G	26,530	1600
			H	25,120	1550
9-Methyl-10-*n*-butylanthracene	c	*n*-Heptane	B	38,390	1290
			E	29,330	1680
			F	27,930	1610
			G	26,490	1640
			H	25,090	1580

TABLE 3—*Continued*

COMPOUND	SOURCE*	SOLVENT	MAXIMUM†	FREQUENCY	SHIFT FROM ANTHRACENE
				$cm.^{-1}$	$cm.^{-1}$
9-Methyl-10-benzylanthracene.....	c	*n*-Heptane	B	38,240	1440
			E	29,410	1600
			F	28,010	1530
			G	26,560	1570
			H	25,090	1580
1,3-Dimethylanthracene...........	f	*n*-Heptane	B	38,990	690
			F	29,160	380
			G	27,780	350
			H	26,280	390
2,9,10-Trimethylanthracene...	f	*n*-Heptane	B	38,170	1510
			E	29,290	1720
			F	27,890	1650
			G	26,490	1640
			H	25,090	1580
		Ethanol	B	38,240	1480
			E	29,240	1650
			F	27,860	1610
			G	26,460	1600
			H	25,060	1580
2,3,9,10-Tetramethylanthracene...	h	Ethanol	B	37,600	2120
			F	27,400	2070
			G	25,970	2090
			H	24,630	2010
1,9-Dimethyleneanthracene........	g	*n*-Heptane	B	38,680	1000
			F	28,130	1410
			G	26,740	1390
			H	25,310	1360
		Ethanol	B	38,760	960
			F	28,130	1340
			G	26,740	1320
			H	25,320	1320
1,2-Trimethylene-5,10-dimethylene-anthracene..............	e	*n*-Heptane	B	38,020	1660
			E	29,110	1900
			F	27,700	1840
			G	26,250	1880
			H	24,870	1800

TABLE 3—*Concluded*

COMPOUND	SOURCE*	SOLVENT	MAXIMUM†	FREQUENCY	SHIFT FROM ANTHRACENE‡
				$cm.^{-1}$	$cm.^{-1}$
1, 2-Trimethylene-5, 10-dimethylene-anthracene—*Concluded*	e	Ethanol	B	38,020	1690
			E	29,150	1740
			F	27,620	1850
			G	26,180	1880
			H	24,880	1760

---

* (a) See table IV of reference 3; (b) Dr. C. F. H. Allen, Eastman Kodak Co.; (c) Dr. E. Berliner, Bryn Mawr College; (d) Dr. L. F. Fieser, Harvard University; (e) Dr. L. F. Fieser and Dr. E. B. Hershberg, Harvard University; (f) Dr. L. F. Fieser and Dr. H. Heymann, Harvard University; (g) Dr. L. F. Fieser and Dr. H. M. Irwin, Harvard University; (h) Dr. L. F. Fieser and Dr. T. Webber, Harvard University; (i) compound synthesized in our own laboratories.

† See figure 1.

‡ See footnote to table 2.

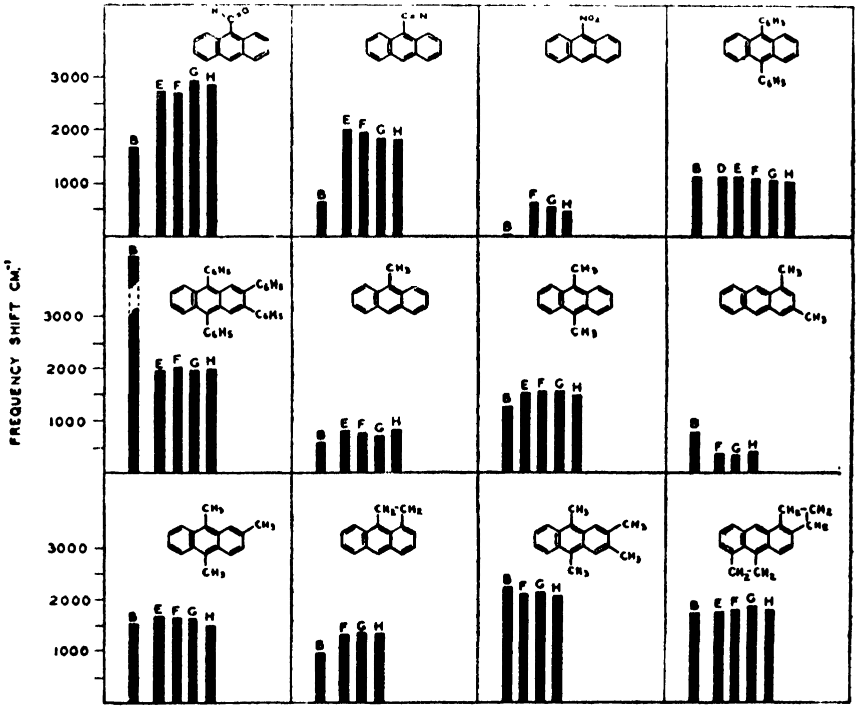

FIG. 11. Diagrammatic representation of frequency displacements of principal anthracene absorption maxima produced by introduction of various substituents.

is well known that the replacement of a hydrogen atom of an aromatic ring system by a methyl group commonly causes a bathochromic displacement of the absorption curve accompanied by little change in the shape of the absorption envelope except for some loss in the resolution of the vibrational fine structure. The positions of the absorption maxima for a variety of alkylanthracenes are listed in table 3, together with the frequency shifts of the principal maxima relative to those of anthracene.

In both 9-methyl- and 9,10-dimethylanthracene the frequency shifts of the A–B maxima differ much less from those of the C–H maxima than is the case for the substituents exhibiting conjugation effects. Thus in the case of 9,10-dimethylanthracene the B maximum is displaced by 1250 cm.$^{-1}$ and the E, F, G, and H maxima by about 1500 cm.$^{-1}$, while the comparable figures for 9-cyanoanthracene are 650 and 1900 cm.$^{-1}$ This uniformity of the bathochromic shifts produced by alkyl substituents in distinction from the selective effects of the conjugatable substituents is illustrated diagrammatically in figure 11, in which the vertical columns are drawn proportional to the frequency displacements caused by introduction of the substituent, the individual maxima being designated by the letter at the top of each column.

The series of compounds 9,10-dimethylanthracene, 9-methyl-10-ethylanthracene, 9-methyl-10-*n*-propylanthracene, and 9-methyl-10-*n*-butylanthracene are included in table 3. The increase in the length of the aliphatic chain of the 10-alkyl group in this series of compounds has an exceedingly small effect on the positions of the maxima, the observed variations being within the limits of experimental error. There is here no indication of any hypsochromic shift on passing from the methyl to a higher alkyl substituent, as has been observed by some investigators (11, 12) in other series of alkylbenzene derivatives.

To account for the effects of these saturated substituents some modification of the argument developed above is needed. In the consideration of the conjugatable substituents, it was tacitly assumed that the whole effect of the substituent was to reduce the energy of the excited state, and that with this action there was associated a selective factor dependent on the alignment of the substituent with respect to certain axes in the molecule. The absorption maxima would also be displaced bathochromically by any change in the molecular structure which would raise the energy of the ground state to a greater extent than it raised the energy of the excited state, and a change of this type, acting primarily on the ground state, would produce a non-selective effect displacing all the maxima by the same amount.

To a first approximation, it would appear that the conjugatable substituents exert their principal action on the spectra by lowering the energy of the excited states, while the alkyl and other non-conjugatable substituents modify the spectra by bringing about an increase in the energy of the ground state. More probably effects of both types are simultaneously active for both types of substituents.[4] Although the 9-alkyl substituents cause displacements of the maxima which are more equal than those of the 9-cyano-, 9-nitro-, and 9-aldehyde groups, there still remains some difference in excess of the experimental error, and this difference is in the same sense as the difference noted for the conjugatable substituents. In 1,3-dimethylanthracene the displacement of the B maximum exceeds by about 300 cm.$^{-1}$ that of the C–H maxima. This difference might be ascribed to some stabilization of the excited states through a hyperconjugation effect, and the magnitude of the difference may be of significance as a rough measure of the extent of such hyperconjugation.

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[4] Views similar to these have been expressed independently by Price (11).

In the case of the conjugatable substituents which exhibit C-effects, the introduction of the substituents will undoubtedly change the energy of the ground

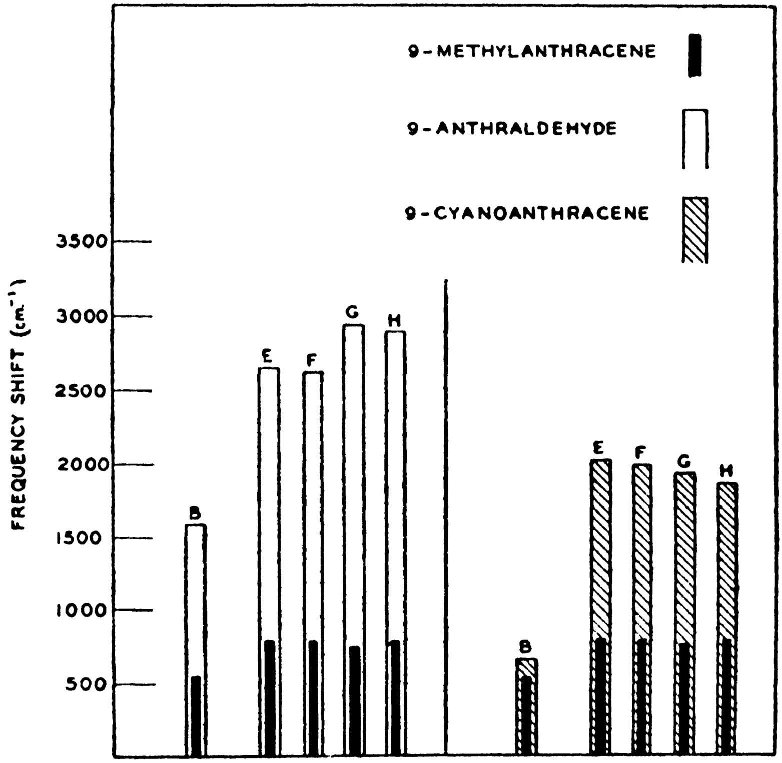

Fig. 12. Frequency displacements of anthracene produced by 9-aldehyde and 9-cyano groups with 9-methyl shifts superimposed.

state to some extent, and if this could be determined and allowed for, the directional specificity of the residual effect on the excited state would appear more pronounced. If the effect of the 9-aldehyde group on the ground state be assumed to be about the same as that of the 9-methyl substituent, and if the hyperconjugation effect of the methyl group be neglected, some idea of the influence of the aldehyde group on the excited state can be derived by subtracting the frequency shifts of the 9-methyl group on each band from that of the 9-aldehyde group. This is shown diagrammatically in figure 12. A similar analysis of 9-cyanoanthracene, also shown in figure 12, would suggest that practically the whole of the displacement of the B maximum in this case might be related to the raising of the energy of the ground state.

IV. CONCLUSIONS

In the semiempirical projection of a theoretical principle beyond the limits of strict or approximate mathematical treatment, it is difficult to decide at what point reasoned argument degenerates into uncritical speculation. In the present instance we are confronted with a considerable body of data on the spectra of complex organic compounds, a comparative study of which enables certain empirical relations to be established. These cannot at present be fitted into a framework of formal mathematical analysis.

Among his many attributes, the late G. N. Lewis possessed the gift of visualizing such complex phenomena in relatively simple terms and in formulating them in such a manner as to suggest new lines of experimental approach. In extending his ideas about the light absorption of complex molecules to the polynuclear aromatic hydrocarbons, it is possible that we have overstepped the bounds of prudent speculation. In defense of the arguments presented in this paper, however, it may be relevant to stress the fact that a better understanding of the structure and spectra of this class of compound is of practical as well as theoretical interest. The highly specific nature of the spectra associated with these ring systems has enabled the organic chemist to make considerable use of ultraviolet spectrometry for the determination of chemical structure. Furthermore, the remarkable ability of certain polynuclear aromatic hydrocarbons to induce cancer has led to an intensive study of their biological activity. In this work it becomes important to detect in living material not only the original hydrocarbons but also the products of their biochemical transformations (4, 5, 15), and such studies will be aided considerably by a better understanding of the effects of small chemical changes on the hydrocarbon spectra.

Most of the data included in tables 2 and 3 have not been published previously, and we therefore wish to take this opportunity of acknowledging our indebtedness to Dr. C. F H. Allen, Dr. E. Berliner, Dr. L. F. Fieser and coworkers, and Dr. R. B. Woodward for their kindness in supplying the compounds used in this investigation. Thanks are also due to Mrs. G. D. Thorn, Mr. A. Cahn, and Miss Kathleen McLean for technical assistance. Part of the work, carried out at Queen's University, Kingston, Ontario, was aided by a grant from The Penrose Fund of The American Philosophical Society.

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THE EFFECTS OF SALTS AND PROTEINS ON THE SPECTRA OF SOME DYES AND INDICATORS[1,2]

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I. INTRODUCTION

Environmental changes frequently produce alterations in spectra which are even more profound than those obtained from modifications in molecular structure. The effects of changes in solvent or physical state have been investigated widely, and much of the pertinent information has been correlated in a review by Sheppard (18). In connection with biochemical studies, an investigation of the effects of salts and proteins on dye spectra are of primary interest, not only because they point out the limitation of colorimetric methods in determining the pH inside microscopic cells, but also because they give an insight into the nature of the interactions between electrolytes, and between proteins and small molecules.

The effects of both salts and proteins can be explained largely on the basis of established thermodynamic principles applicable to ionic equilibria. Some recourse must be made, however, to specific interactions, the nature of which is not yet entirely clear.

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[1] Presented at the Symposium on Color and the Electronic Structure of Complex Molecules which was held under the auspices of the Division of Physical and Inorganic Chemistry of the American Chemical Society at Northwestern University, Evanston and Chicago, Illinois, December 30 and 31, 1946.

[2] Most of the work on salt effects was carried out in cooperation with Dr. C. R. Singleterry under the direction of Professor T. F. Young at the University of Chicago

II. SALT EFFECTS

It has long been realized that colorimetric methods give erroneous pH values in solutions of high salt content (23). Such errors can be traced back fundamentally to spectral shifts upon addition of the electrolyte. A typical example of such a shift is illustrated for the indicator methyl orange in figure 1. Extensive studies of these shifts under a wide variety of conditions have shown that these "salt errors" may be attributed to one or more of the following factors: (*1*) changes in the absorption spectrum of one or both forms of the indicator dye; (*2*) a shift in equilibrium between acid and base forms of the indicator due to electrostatic interactions; (*3*) changes in pH of the medium due to removal of some hydrogen ion by combination with the salt. The last effect is quite pronounced even with salts, such as sodium sulfate, which generally are not considered to change the pH appreciably. Careful investigations of all of these effects have given not only information on the properties of the dyes but also a much clearer insight into the nature of ionic interactions in aqueous solutions.

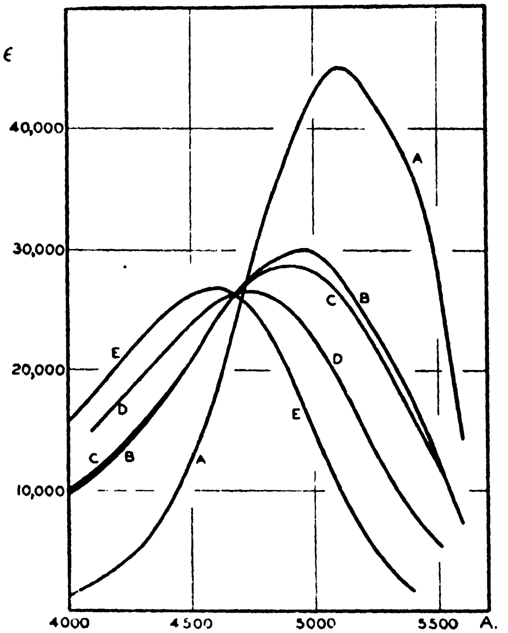
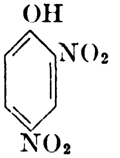


FIG. 1. Salt effects on spectra of methyl orange. A, indicator in solution of hydrochloric acid, pH 1.98; B, indicator in solution of hydrochloric acid, pH 3.51; C, indicator in solution B with addition of potassium chloride to give 0.25 molar solution; D, indicator in solution B with addition of sodium sulfate to give 0.06 molar solution; E, indicator in phosphate buffer, pH 7.73.

A. Changes in spectra of end forms of indicator dye

The most precise optical investigations of the effect of a salt on the spectrum of an end form of an indicator are those of von Halban and Kortüm (8, 25).

Having at their disposal a differential spectrophotometer capable of a precision of better than 0.01 per cent, these investigators studied the effects of numerous salts in exceedingly dilute solution (*ca.* 10^{-4} molar). The dependence of spectral shifts of the dinitrophenolate ion on the charge type of the added electrolyte is illustrated in figure 2. The very large increase in absorption with di- and trivalent ions is particularly striking. It is also of interest to note that the uni-univalent salts affect the absorption in a manner opposite to that observed with the polyvalent ions. Spectral shifts are observed also in dilute solution of added non-electrolyte such as urea.

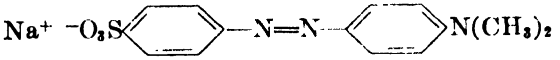


I

2,4-Dinitrophenol

There seems to be no relation between the magnitude of the spectral shift and the activity coefficient of the added ion. Consequently, the optical changes in the dinitrophenolate ion cannot be attributed to ion-cloud interactions of the Debye–Hückel type (8). An explanation in terms of ion association also seems unlikely, because anions are capable of causing deviations equal in magnitude to those observed with cations. Optical variations seem to be determined rather by interactions between added ions and the solvent molecules surrounding the light-absorbing ion (8). Such a conclusion is substantiated by the correlation between the magnitude of shift produced by a given ion and the value of its hydration energy.

An ion such as that of 2,4-dinitrophenol would be particularly sensitive to electrolyte–solvent interactions, since the dye has three highly exposed polar groups which must interact strongly with the solvent molecules and which simultaneously are intimately involved in the resonance which determines the stability of the ground and excited states of the molecule. Somewhat smaller effects might be expected for the end forms of methyl orange (II) with fewer highly polar substituents. Figure 3 summarizes some of the effects observed with methyl orange by Sidgwick, Worboys, and Woodward (20). The deviations are somewhat less than those for sodium perchlorate on dinitrophenol and specific anion effects are not observable.



II

Methyl orange

B. Effects on activity coefficients of indicators

From figure 3 it is obvious that the large salt deviations illustrated in figure 1 cannot be attributed to changes in the spectra of the end forms of methyl orange, for such changes are negligibly small at concentrations of electrolyte near 0.1 molar. The effect of a completely unhydrolyzed salt, such as potassium chloride, must be ascribed, therefore, to electrostatic interactions which alter the equilibrium between acid and base forms of the indicator. Such an explanation in terms of ion-cloud interactions can account for the magnitude of the deviations observed, and in the limit of the infinitely dilute solutions, leads to excellent agreement between observed behavior and that predicted by the Debye-Hückel theory.

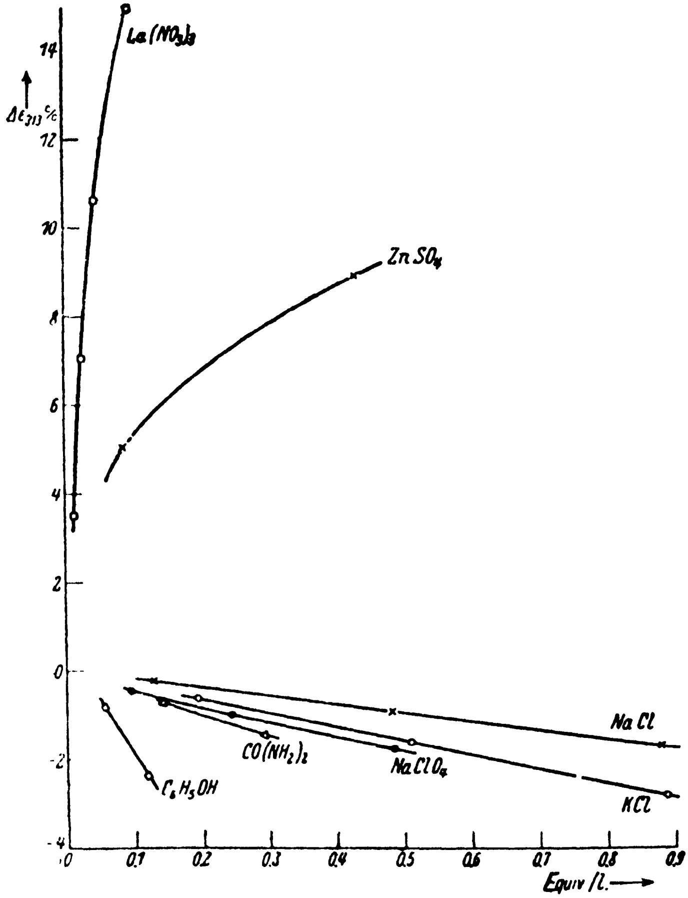


FIG. 2. Effect of various substances on the optical absorption of the 2,4-dinitrophenolate ion.

Since the behavior observed with methyl orange is typical of a large number of indicators, we may generalize our analysis by the following notation: If we allow the acid form of the indicator to be represented by HI, then the dissociation equilibrium may be described by the equation:

$$HI = H^+ + I^- \tag{1}$$

The corresponding equilibrium constant, K, would be expressed by the relation

$$\frac{(\mathrm{H}^+)(\mathrm{I}^-)}{(\mathrm{HI})}\,\frac{\gamma_{\mathrm{H}^+}\gamma_{\mathrm{I}^-}}{\gamma_{\mathrm{HI}}} = K \tag{2}$$

where the parentheses represent molar concentrations and γ's the activity coefficients. Conversion of equation 2 to the logarithmic form leads to:

$$\log \frac{(\mathrm{I}^-)}{(\mathrm{HI})} = \log K - \log (\mathrm{H}^+) - \log \frac{\gamma_{\mathrm{H}^+}\gamma_{\mathrm{I}^-}}{\gamma_{\mathrm{HI}}} \tag{3}$$

The spectrum, or color, of the indicator solution is determined by the ratio $(\mathrm{I}^-)/(\mathrm{HI})$. From equation 3 it is clear that this ratio can be affected only by a change in (H^+) or in the activity coefficient ratio. Since a salt such as sodium chloride or potassium chloride does not change the hydrogen-ion concentration, the addition of an electrolyte of this type to the indicator solution affects only the activity ratio. From variations of color, and hence of $(\mathrm{I}^-)/(\mathrm{HI})$, it is possible, therefore, to evaluate the activity-coefficient ratio at various ionic strengths. A typical set of such investigations for methyl orange (4, 21) is illustrated in figure 4. It is interesting to observe that the activity coefficients are practically the same in solutions of barium chloride as of sodium chloride, despite the change in charge type. Apparently this manifestation of specific ion interactions is also rather small in methyl orange. For both of these salts, the activity-coefficient ratio increases (in absolute magnitude) with increasing temperature, a

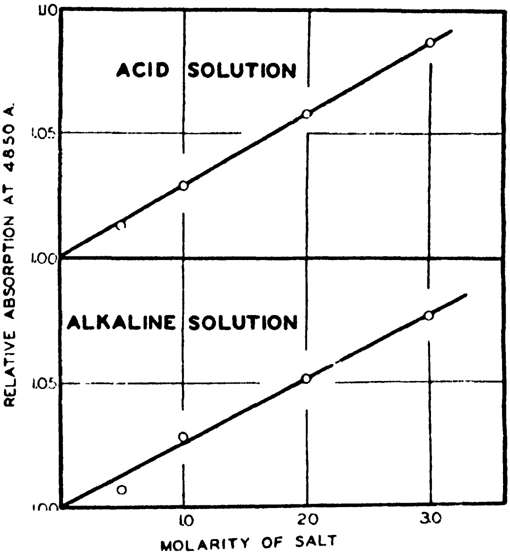


FIG. 3. Effect of salts (sodium chloride, sodium bromide, sodium chlorate, sodium nitrate, potassium chloride, potassium bromide) on light absorption of end forms of methyl orange (20).

behavior characteristic of electrolytes. The shapes of the curves also indicate an increase in the magnitude of the limiting slope, in agreement with the Debye-Hückel theory. At 25°C. a least-squares equation through the sodium chloride data yields, upon differentiation, a limiting slope of -1.09, a value which is in satisfactory agreement with the theoretical one of -1.02. Since the method is capable of giving the limiting slope only within about 10 per cent, it is impossible to make any quantitative comparison with the theoretical prediction of a 9 per cent change between 5° and 55°C., but an inspection of figure 4 indicates good qualitative agreement.

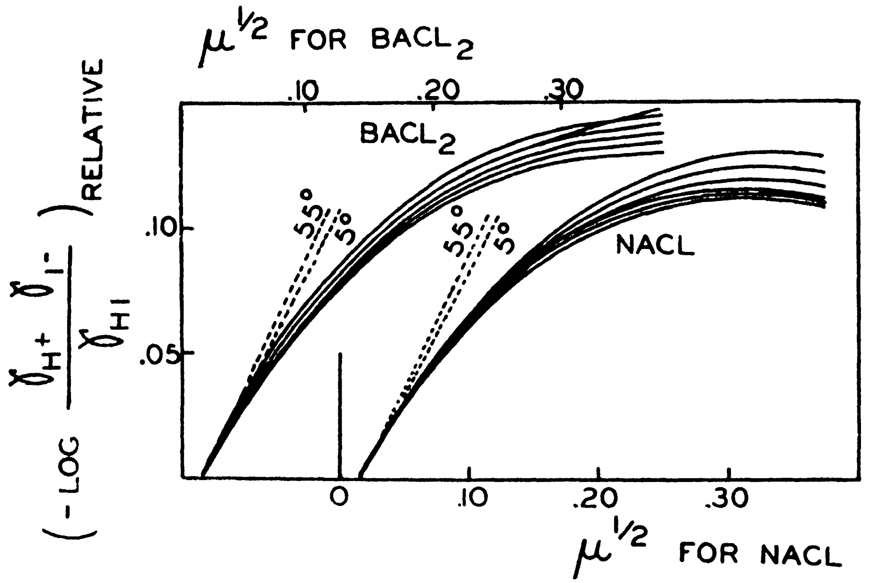
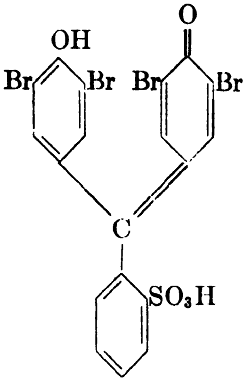


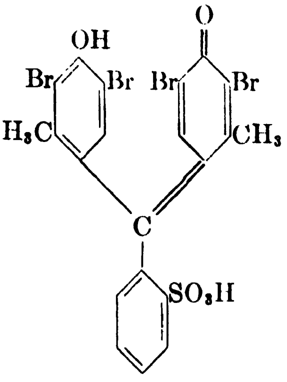
FIG. 4. Activity coefficient ratio (relative to reference solution) for methyl orange in solutions of sodium chloride and barium chloride, respectively. In each case the lowest curve is for 4.7°C., the others at higher temperatures, in intervals of 10°. The dotted lines represent the Debye-Hückel limiting slopes at the temperatures indicated (4, 21).

C. Removal of hydrogen ions by salts of moderately strong acids

It has been realized for some time, of course, that color changes may occur in an indicator solution upon the addition of a salt of a weak acid, e.g., sodium acetate, since acetate ions remove some hydrogen ions. As is obvious from equation 3, the ratio $(I^-)/(HI)$ is affected by changes in pH even if the activity ratio is held constant. That such pH changes might be detectable in dilute acid solutions upon the addition of sodium sulfate, a salt of a moderately strong acid, HSO_4^- ion, was not evident until some observations made by Mullane (12). He found that the addition of alkali metal sulfates to solutions of the indicators bromophenol blue (III) or bromocresol green (IV) produces changes in color which are far greater than the consistently uniform results obtained with alkali



III
Bromophenol blue



IV
Bromocresol green

metal chlorides, bromides, or nitrates. Bromophenol blue and bromocresol green, however, show large neutral salt errors, because the equilibria between acid and base forms involve ions of single and double charge, and hence are not suitable for evaluating the ionization constant of HSO_4^- ion from pH deviations. On the other hand, the neutral salt effects with methyl orange are relatively small (figure 4); hence the large pH deviations upon the addition of sulfates (figure 5) offer a convenient method of determining the ionization constant of a moderately strong acid such as the bisulfate ion.

The equilibrium constants for the reaction

$$HSO_4^- = H^+ + SO_4^{--} \tag{4}$$

calculated (4, 21) from the data summarized in figure 5 are listed in table 1, together with the values of related thermodynamic quantities. For the dissociation in question the constants obtained are probably the most accurate available. Earlier electromotive-force investigations (3) of the bisulfate dissociation gave results which must certainly be erroneous, since they lead to a heat of dissociation at 25°C. of -2229 cal. per mole, a value in gross disagreement with the direct calorimetric determination of -5200 cal. per mole (14). There are indications that the extrapolation methods involved in the E.M.F. procedures break down with moderately strong acids having ionization constants near 10^{-2}.

Optical deviations in solutions of methyl orange can be used also to determine dissociation constants of other moderately strong acids besides bisulfate ion. As with bisulfate ion, changes of optical absorption upon addition of the electrolyte are corrected for neutral salt effects by reference to curves for sodium chloride or barium chloride and the remainder of the deviation is attributed to changes in hydrogen-ion concentration. The results obtained with chloroacetic acid are compared in table 2 with values given in the literature. The agreement between the two optical methods is very good, but both of these differ significantly from the results obtained by classical electrical techniques.

The optical method described in this paper is particularly suitable for the determination of the dissociation constants of the carboxyl groups of the amino acids (27), for the measurements can be made in solutions of very low ionic strength (*ca.* 5 × 10^{-4}) where the Debye-Hückel limiting law may be used as a close approximation to the activity coefficients of the ions. In consequence the

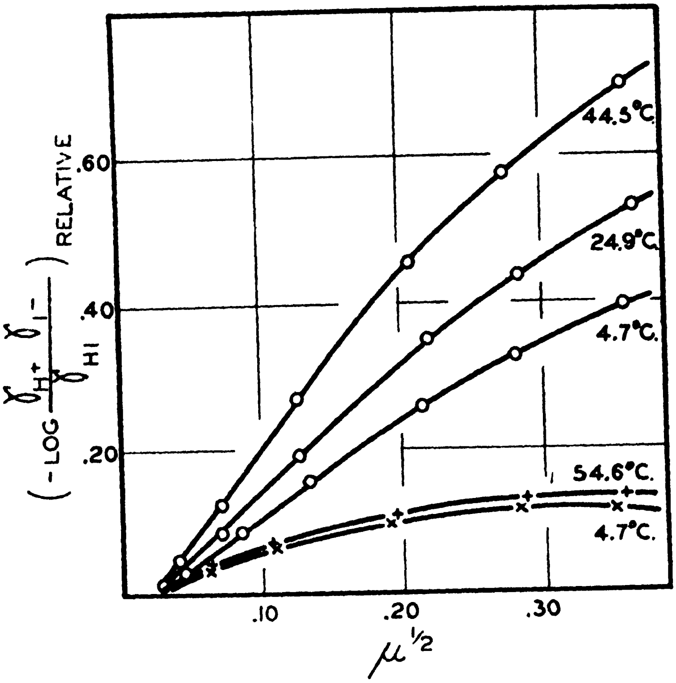


FIG. 5. Salt effect of sodium sulfate on absorption of methyl orange as a function of temperature: ○, sodium sulfate; +, ×, sodium chloride.

TABLE 1

Thermodynamics of ionization of HSO_4^- (*4, 21*)

TEMPERATURE	K	ΔF^0	ΔH^0	ΔS^0
°C.		*cal./mole*	*cal./mole*	*cal./mole degree*
5	0.0180	2220	−4270	−23.3
25	0.01015	2720	−5190	−26.5
45	0.00558	3280	−6110	−29.5

extrapolations required involve an almost horizontal line and lead to high precision in the end result (table 3).

III. PROTEIN EFFECTS

Early interest in color changes produced by proteins arose, as in the case of salt effects, in connection with pH determinations (22). Recently it has also been shown that spectral variations offer a very useful approach to the problem of protein interactions with small molecules (5, 7).

Analysis of the basic causes of protein errors in colorimetric pH determinations indicates that four mechanisms are most important in creating these deviations: (*1*) the protein may disturb micelle equilibria; (*2*) the protein may adsorb an indicator ion of opposite charge, aided by electrostatic attraction, and thereby disturb the equilibrium between the acidic and basic forms of the indicator; (*3*) specific attractive forces may lead to complex formation between the protein and indicator ion even when both have the same electrical charge and hence a strong electrostatic repulsion; and (*4*) the spectrum of the dye in combination with the protein may differ substantially from that of the free dye.

TABLE 2

Ionization constant of chloroacetic acid

METHOD	*K*	TEMPERATURE	REFERENCE
		°C.	
Conductance	1.396×10^{-3}	25.0	(16, 17)
E.M.F.	1.378×10^{-3}	25.0	(26)
Optical (M,K)*	1.337×10^{-3}	25.0	(11)
Optical (Y,K,S)	1.316×10^{-3}	24.8	(4, 21)

* The optical method of Minnick and Kilpatrick depends on a knowledge of the dissociation constant of the indicator. The indicator constant does not enter into our calculations.

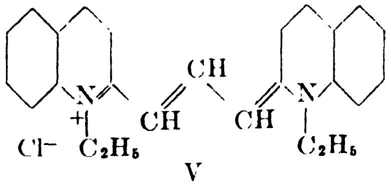
TABLE 3

Ionization constant of carboxyl group of glycine

METHOD	*K*	TEMPERATURE	REFERENCE
		°C.	
E.M.F.	4.47×10^{-3}	25.0	(13)
Optical	4.46×10^{-3}	25.0	(27)

A. Effects on micelle equilibria

A typical example of the disturbance of dye micelle equilibria is illustrated in the work of Sheppard and Geddes (19), exhibited in figure 6. From investigations of deviations from Beer's law, Sheppard and Geddes concluded that the dye pinacyanol (V) exists partially in the dimeric state in aqueous solution.



V

Pinacyanol chloride

The addition of gelatin tends to break up this dimerization and hence changes the spectrum toward that characteristic of the monomer. The addition of the cationic detergent cetylpyridinium chloride produces an optical effect similar to that of gelatin. Again there is a tendency to break up the dimer. The interaction between dye and protein or detergent, respectively, seems to be between organophile portions of the molecules. Since the cyanine dye is cationic no electrostatic attraction would exist, for the gelatin used was one of high isoelectric point (8.8) and hence it too was cationic at the pH used (5.6).

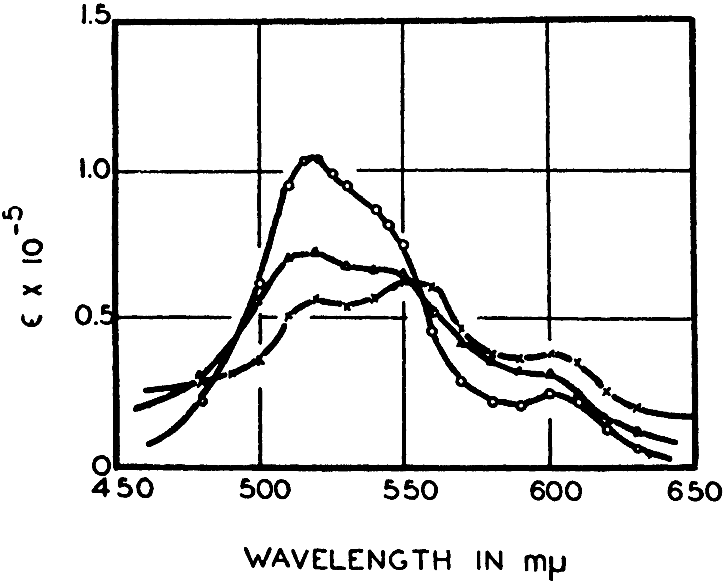


FIG. 6. Absorption spectra of pinacyanol: O, in aqueous solution; X, in aqueous solution containing cetylpyridinium chloride; △, in aqueous solution containing gelatin (19).

B. Combination of protein with dye ion of opposite charge

Protein effects on an indicator such as methyl orange cannot be attributed to disturbance of micelle equilibria, since methyl orange obeys Beer's law in dilute solutions (figures 7 and 8). Nevertheless, colorimetric pH determinations with methyl orange in the presence of proteins are frequently grossly in error. The magnitude of such deviations is best illustrated by the work of Thiel and Schulz (24), shown in figure 9. Errors over one pH unit are observed in solutions of egg albumin even at concentrations below 0.5 per cent.

Since methyl orange does not exist in a polymeric state in dilute aqueous solution, the optical deviations in the presence of proteins must be attribtued to a disturbance of the acid-base equilibrium symbolized by equation 1. Such a disturbance seems very plausible, in view of the fact that the isoelectric points of casein and egg albumin are near pH 5. At pH's below 5, both of these proteins would be positively charged and hence would exert a strong electrostatic attraction on the methyl orange anion, I^-. Reference to equation 1 shows that the combination of protein with I^- would decrease the concentration of HI and hence shift the spectrum toward the anionic form.[3] To return the spectrum toward the protein-free type obviously would require the addition of acid, as has been observed by Thiel and Schulz (24) (figure 9).

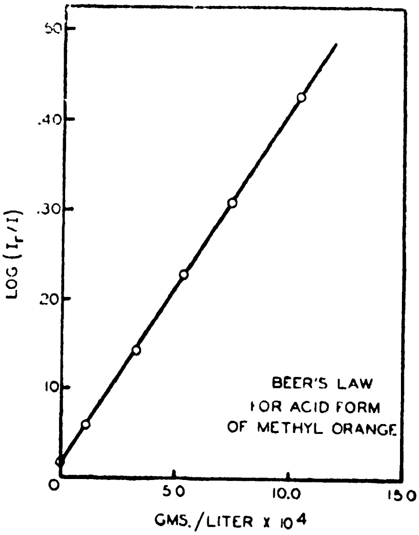


Fig. 7. Optical absorption of methyl orange as a function of concentration, in acid solutions.

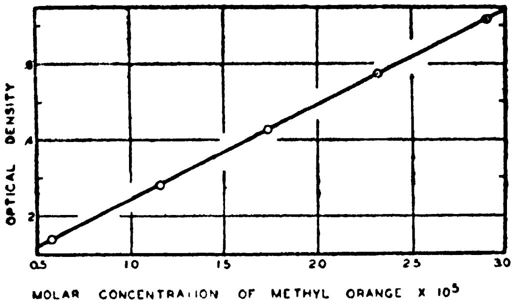


Fig. 8. Optical absorption of methyl orange as a function of concentration in solutions of pH 5.7.

In view of this interpretation of the basis of the spectral changes of methyl orange in the presence of proteins such as egg albumin, one would expect optical deviations to disappear at pH's above 5, since the protein begins to acquire a negative charge. This prediction cannot be tested with methyl orange, because this indicator would be almost completely in the anionic form at pH 5, since its p*K* is near 3.5. On the other hand, bromocresol green (IV) can be examined in this region, since its p*K* is 4.92 (12), and in view of the fact that its colored forms are anionic, its behavior should be similar to that of methyl orange. The pH error for bromocresol green in the presence of egg albumin has been investigated by Danielli (2). The experimental observations (figure 10) are in agreement with expectation, in that the protein error is large in highly acid solution, decreases with increasing pH, and becomes essentially zero after the isoelectric

---

[3] This assumes that the anion has the same spectrum in the free and in the combined state. As will be shown later, such is not quite the case, but the changes due to combination of methyl orange with the protein are much smaller than those accompanying the addition of a hydrogen ion.

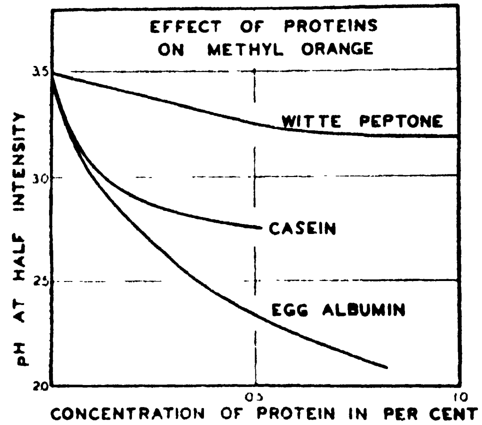


Fig. 9. Colorimetric pH errors of methyl orange in the presence of proteins (24)

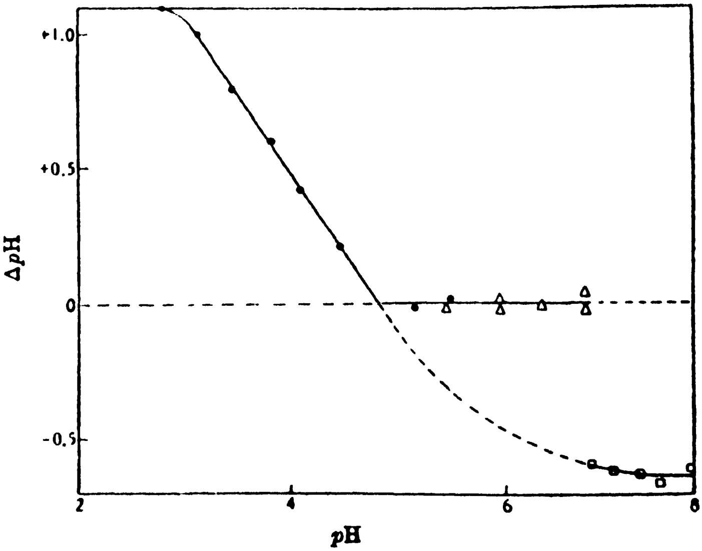
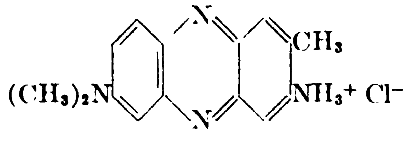
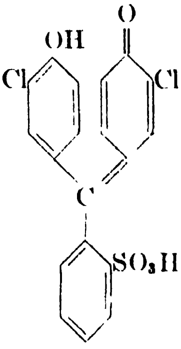


Fig. 10. Colorimetric pH errors in the presence of egg albumin: ●, bromocresol green; △, chlorophenol red; □, neutral red (2).

point of egg albumin has been attained. Similarly it is interesting to note in figure 10 that neutral red (VI), a cationic indicator, is affected by egg albumin in the pH range above 5 where the protein is negatively charged and can attract the cation electrostatically. The absence of electrostatic attraction would account for the lack of a protein error in the case of chlorophenol red (VII) (figure 10).



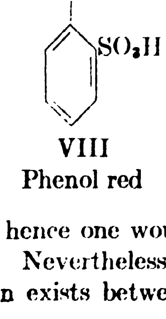
VI
Neutral red



VII
Chlorophenol red

C. Formation of complexes between protein and dye ion of same charge

While the theory of electrostatic attraction of oppositely charged entities accounts for the spectral deviations in the presence of many proteins, there are some situations in which this interpretation is obviously inadequate. Thus, Lepper and Martin (9) have observed an appreciable colorimetric deviation for phenol red (VIII) upon the addition of serum albumin (figure 11). This protein is anionic at pH's above 5; hence one would expect no electrostatic interaction with an anionic indicator. Nevertheless the observed colorimetric errors suggest that a specific attraction exists between the serum albumin and this



VIII
Phenol red

anionic indicator and that the resultant complex causes a displacement of the acid–base equilibrium.

The possibility of a protein–anion combination even when both species are anionic was investigated by studying the binding of methyl orange anions by serum albumin at pH's above 5. Some typical results obtained by a dialysis–

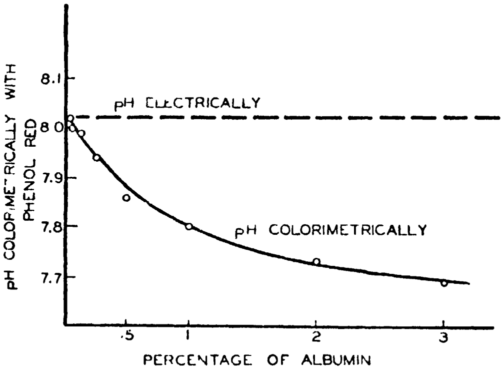


FIG. 11. Colorimetric pH errors of phenol red in the presence of serum albumin (9)

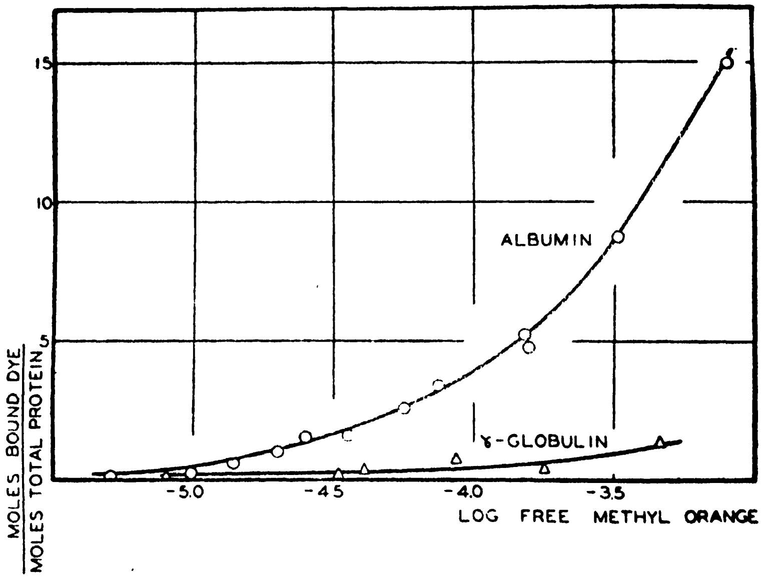


FIG. 12. Binding of methyl orange by serum proteins at pH 5.7

distribution technique are illustrated in figure 12. Clearly, very large fractions of the indicator anion combine to form a complex with the albumin even in solutions of the order of 10^{-5} molar. Such complex formation could have a pronounced effect on the equilibrium between the acid and base forms of an indicator with a pK near the pH range studied.

Formation of complexes between albumin and a dye ion of the same charge is not limited to methyl orange anions. Quantitative determinations of the degree of binding have been obtained by dialysis–distribution studies with orange I (IX), orange II (X), azosulfathiazole (XI), amaranth (XII), and bromocresol green (IV). Qualitative evidence is available for a large number of other anionic dyes (5, 6).

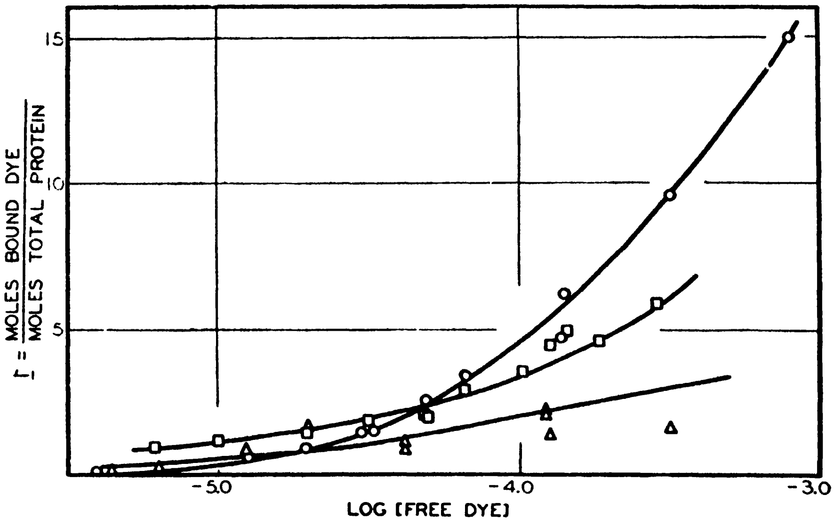
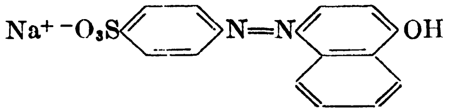
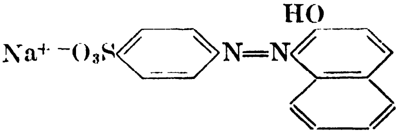


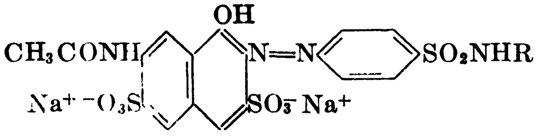
Fig. 13. Binding of sulfonate compounds by bovine serum albumin at pH 5.7; ○, methyl orange (II); □, azosulfathiazole (XI); △, amaranth (XII).



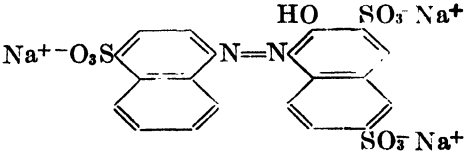
IX
Orange I



X
Orange II



XI
Azosulfathiazole
(R = thiazole ring)



XII
Amaranth

The quantitative data on the binding of methyl orange, azosulfathiazole, and amaranth, respectively, are presented together for comparison in figure 13. One of the most striking characteristics in this figure is the decrease in the curvature as the number of negative charges on the anion increases from 1 to 3. Since decreasing curvature corresponds to less binding relative to that observed in a very dilute solution, it is apparent that the electrostatic repulsion between dye anion and negatively charged albumin becomes increasingly important as the number of charges on the dye increases. Such behavior would be expected, of course, from the principles of electrostatics. In fact, one can express these predictions in quantitative terms if one formulates the proper expression for the law of mass action for such cases of multiple binding.

It is obvious from figures 12 and 13 that more than one molecule of dye may be bound by one protein molecule. If we let P represent the protein and A the dye anion, then the successive equilibria involved may be expressed by the equations

$$\begin{aligned} \mathrm{P} + \mathrm{A} &= \mathrm{PA} \\ \mathrm{PA} + \mathrm{A} &= \mathrm{PA_2} \\ &\cdots\cdots\cdots\cdots \\ \mathrm{PA}_{n-1} + \mathrm{A} &= \mathrm{PA}_n \end{aligned} \tag{5}$$

where n is the maximum number of anions which a protein molecule can bind. The equilibrium constant for any step in equations 5 may be determined from the relation:

$$\frac{(\mathrm{PA}_i)}{(\mathrm{PA}_{i-1})(\mathrm{A})} = k_i \tag{6}$$

It has been shown (7) that the ratio, r, of the moles of bound anion to the total moles of protein is given, for the general case, by the equation:

$$r = \frac{\sum_{i=1}^{n} i\left(\prod_{j=1}^{i} k_j\right)A^i}{1 + \sum_{i=1}^{n}\left(\prod_{j=1}^{i} k_j\right)A^i} \tag{7}$$

To determine r as a function of the anion concentration, A, it is obviously necessary to have information on the equilibrium constants, k_i.

The simplest situation that one might encounter in protein binding is that in which each anion is bound to the same kind of group on the protein and in which a bound ion exerts no electrostatic influence on succeeding bindings. In such a situation, the strength of attachment would be the same for each bound anion. Hence the relative values of the successive equilibrium constants would be determined solely by statistical factors and would be given by the relation:

$$k_i = \frac{n - (i - 1)}{i}\,\frac{1}{K} \tag{8}$$

K is a specific binding constant which depends on the nature of the anion as well as on the character of the protein. Where the statistical effect is predominant and the equilibrium constants are given by equation 8, the relatively involved equation 7 may be reduced to a very simple linear form:

$$\frac{1}{r} = \frac{1}{n}\left[\frac{K}{(\mathrm{A})} - 1\right] \tag{9}$$

This statistical relation is a very good approximation to the quantitative data on the binding of the singly charged anionic dyes, methyl orange, orange I, and orange II, respectively, as is evident from figure 14. Apparently each focus of attachment on the albumin molecule must have the same inherent tendency for attaching an anion of any given one of these dyes.

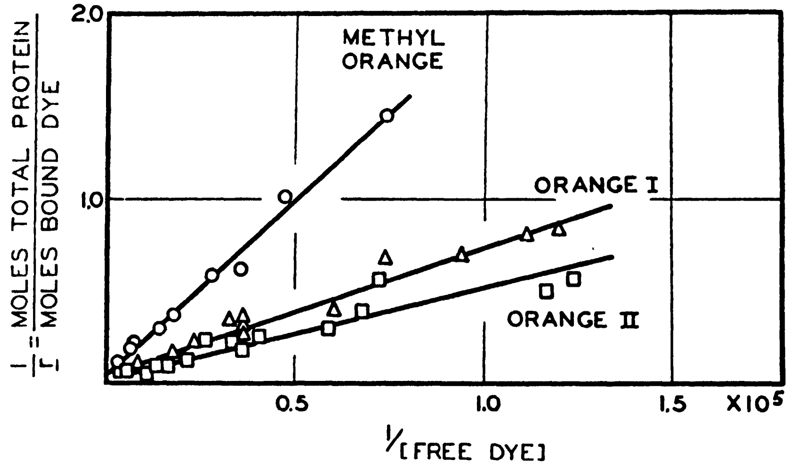


FIG. 14. Binding of some singly charged dyes by serum albumin at pH 5.7

For dyes with two and three charged groups, the statistical distribution of constants is unable to account for the actual behavior. It is necessary to take electrostatic interactions into account. It is perhaps easiest to visualize the nature of the electrostatic effect by introducing it in terms of the free energy of the binding process for the i^{th} step:

$$\Delta F^0 = -RT \ln k_i = \Delta F_{\mathrm{stat}} + \Delta F_{\mathrm{specific}} + \Delta F_{\mathrm{elect}} \tag{10}$$

ΔF_{stat} represents the statistical contribution to the change in free energy; ΔF_{spec} the contribution of the intrinsic binding constant K; and $\Delta F_{\mathrm{elect}}$, the contribution of electrostatic interactions. The electrostatic contribution may be evaluated in terms of the charging energy of an ion in an electrolyte solution. To focus attention on the effect of the charge of the anion alone it is convenient to consider the transfer of one dye ion from one complex to another of lower degree, as is represented in the equation:

$$\mathrm{PA}_i + \mathrm{PA}_{i-2} = 2\mathrm{PA}_{i-1} \tag{11}$$

For this reaction the electrostatic free-energy change is given by the expression

$$\Delta F_{\mathrm{elect}} = -\frac{Nz^2e^2}{D}\left(\frac{1}{b} - \frac{\kappa}{1 + \kappa a}\right) \tag{12}$$

where N is Avogadro's number, z is the number of charges on A, e is the electronic charge, D is the dielectric constant of the medium, b is the radius of the protein molecule, a is the "distance of closest approach" of a charged ion to the protein, and κ is given by

$$\kappa = \left(\frac{4\pi N e^2}{1000 D k' T}\right)^{\frac{1}{2}} \Gamma^{\frac{1}{2}} \tag{13}$$

where k' is the Boltzmann constant, T is the absolute temperature, and Γ is twice the ionic strength of the medium.

From equation 12 it is clear that the electrostatic effect, depending on the square of z, becomes increasingly important with increasing charge on the anion. Since the anion and protein have the same charge, the electrostatic interaction is a repulsive one and the protein tends to bind fewer of the more highly charged anions, as the anion concentration increases. Thus the curvature of the graphs in figure 13 should be less for azosulfathiazole (two SO_3^-'s) than for methyl orange (one SO_3^-), and that for amaranth (three SO_3^-'s) should be smallest. The observed behavior is not only in qualitative agreement with the theoretical explanation but also quite close quantitatively. By making reasonable choices for the radii of the protein and of the dye anions it is possible to calculate the electrostatic free-energy change from equation 12. This information, in addition to an empirical evaluation of a single constant, K, the intrinsic binding constant, enables one to evaluate the individual constants, k_i, and ultimately r, the moles of bound anion per mole of total protein. Quite satisfactory agreement has been found between the theoretical curves so calculated and the observed experimental values.

D. Changes in spectra of dye–protein complexes

1. Dependence on nature of dye

In addition to displacing acid–base equilibria in indicators, proteins may cause optical deviations by changing the spectrum of the bound form of the dye. Such an alteration is illustrated in figure 15 for methyl orange in the presence of serum albumin. While the displacement is not great, there is a distinct lowering of the maximum absorption and a shift of the peak by about 200 A. Similar results are obtained with orange I (figure 16), azosulfathiazole (figure 17), and amaranth (figure 18). While the addition of bovine albumin lowers the value of the maximum extinction coefficient in each of the above azo compounds, the shift in the wave length of the absorption peak is not the same in each case (table 4). Thus the complexes with azosulfathiazole and amaranth, respectively, have their peaks shifted to longer wave lengths, whereas those with orange I and orange II, respectively, show no significant displacement. Apparently the relative effect of the protein on the energies of the ground and excited states of the dyes is dependent on the nature of the entire molecule, and not only on the character of the binding sulfonate group.

It is important, of course, to prove that these spectral displacements are due to actual binding of the dye anion by the serum albumin. Since an alternative explanation would be the displacement of the polymer equilibria by the protein,

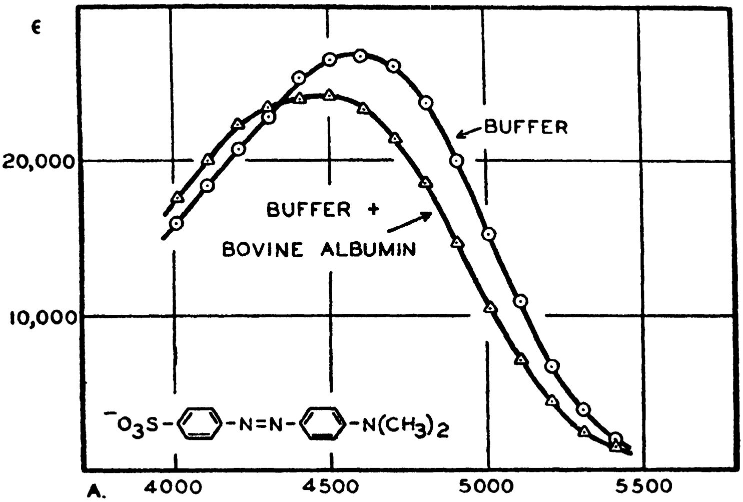


FIG. 15. Effect of serum albumin on spectrum of base form of methyl orange

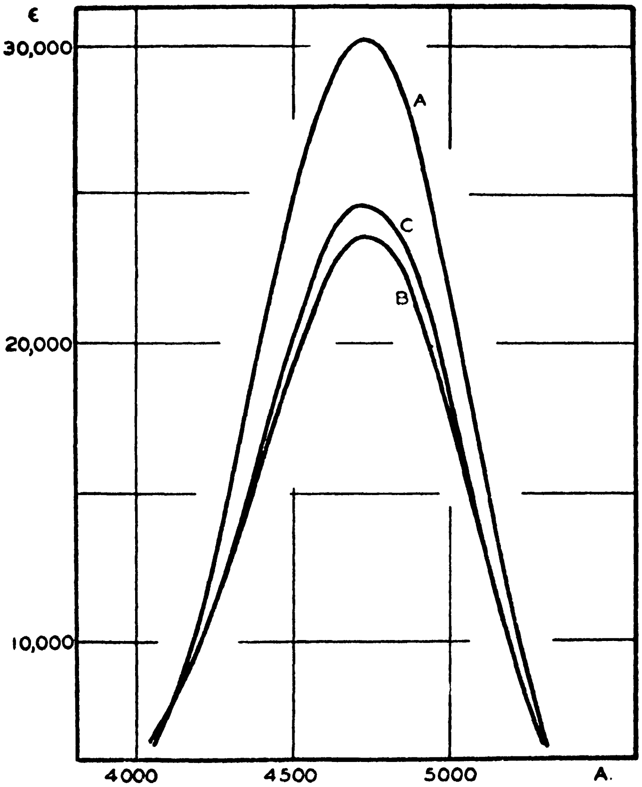


FIG. 16. Absorption spectra of Orange I: A, in buffer at pH 6.8; B, in buffer containing bovine albumin; C, in buffer containing bovine albumin and potassium acid phthalate.

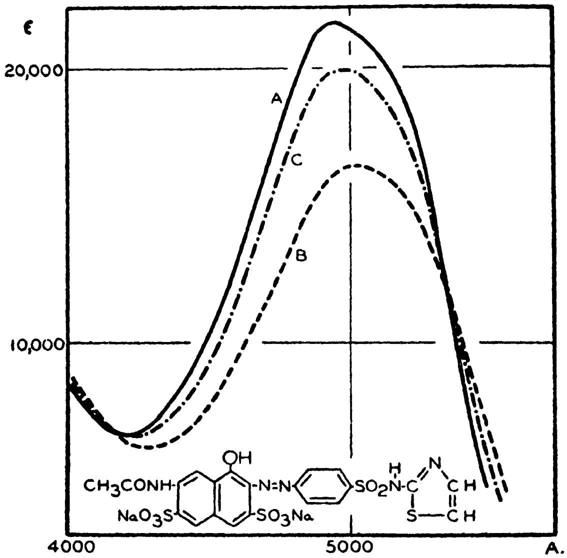


FIG. 17. Absorption spectra of azosulfathiazole: A, in buffer at pH 6.8; B, in buffer containing bovine albumin; C, in buffer containing bovine albumin and potassium acid phthalate.

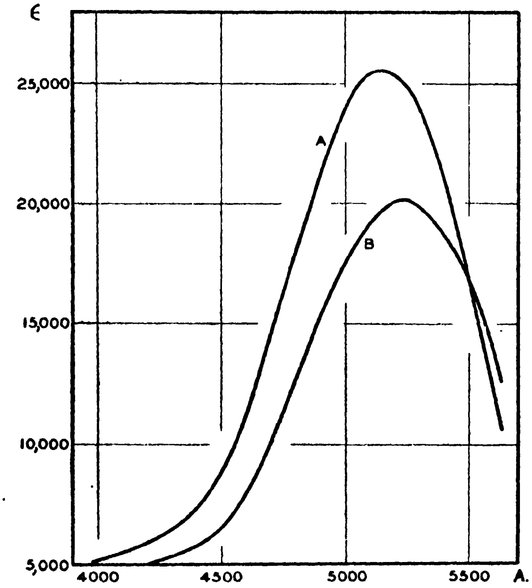


FIG. 18. Absorption spectra of amaranth: A, in buffer at pH 6.9; B, in buffer containing bovine albumin.

the adherence to Beer's law was investigated for each dye. Linear dependence of optical absorption upon concentration was observed in every case up to concentrations of at least 10^{-4} molar; hence the possibility of dimerization has been ruled out. This interpretation also seemed unlikely when it was found that micellar sodium dodecyl sulfate did not produce spectral displacements even in 1 per cent concentration, a quantity which is almost five times as much as is necessary to produce a maximum effect with bovine albumin.

TABLE 4

Effect of bovine serum albumin on the position of absorption peak

DYE	ABSORPTION PEAK IN BUFFER	ABSORPTION PEAK IN PRESENCE OF PROTEIN
	A.	A.
Methyl orange	4600	4400
Orange I	4730	4730
Orange II	4810	4810
Azosulfathiazole	4950	5050
Amaranth	5140	5240

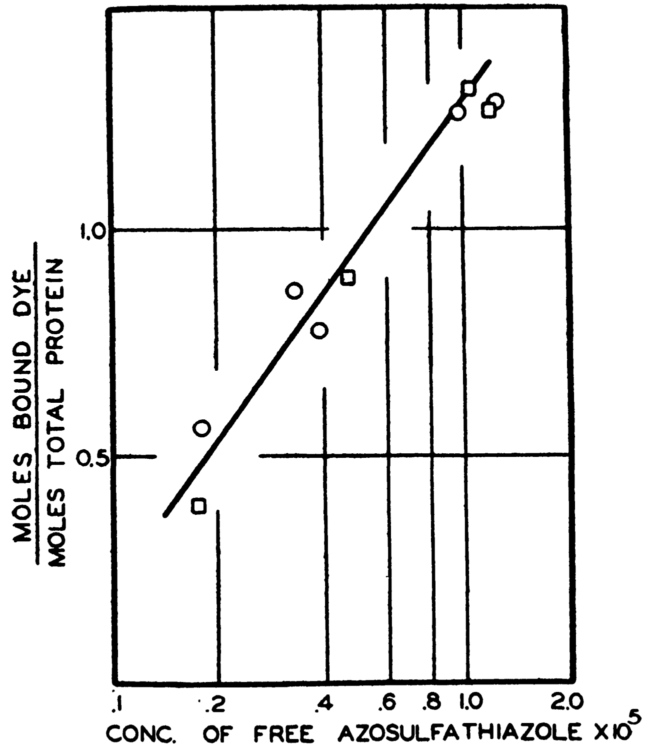
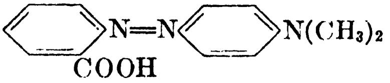


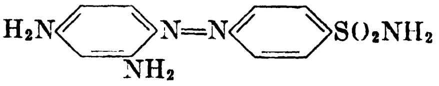
FIG. 19. Quantitative data on the extent of binding of azosulfathiazole: ○, from spectral measurements; □, from dialysis-equilibrium studies.

Direct evidence that the spectral displacements are due to binding was also obtained by calculating the extent of binding from optical changes in solutions of varying protein and dye concentrations (5). The results obtained in this fashion agree very well (figure 19) with those obtained by the direct dialysis-distribution method. Thus there is no question but that the spectral shifts are a result of formation of complexes between the dye and protein molecules.

It is not essential for binding by albumin that the dye have a sulfonate group. Similar results (figure 20) are obtained with methyl red (XIII), which has a carboxyl group. Apparently, however, an anionic substituent is essential for *strong* binding by albumin, for prontosil (XIV), which lacks such a group, shows only small spectral changes.



XIII
Methyl red



XIV
Prontosil

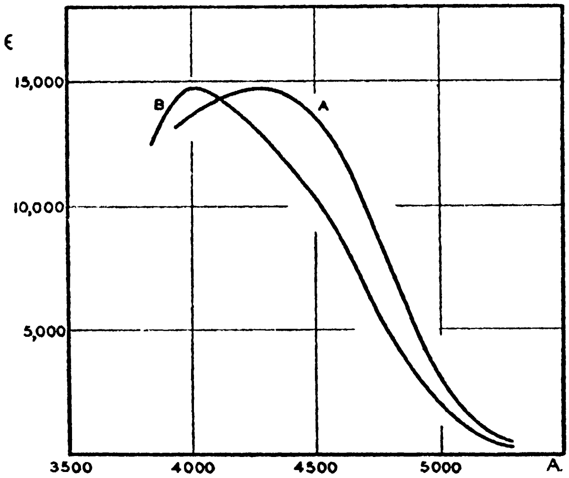


FIG. 20. Absorption spectra of methyl red: A, in buffer at pH 7.3; B, in buffer containing bovine albumin.

So far, spectral deviations have been observed only with serum albumin, bovine or human. No significant effects are obtained with γ-globulin, gelatin, egg albumin, or casein. Apparently these proteins, basic to their isoelectric points, are incapable of binding the dyes. The absence of appreciable binding has been confirmed for γ-globulin by dialysis techniques. Only in concentrated solutions is a significant quantity of methyl orange bound (figure 12) and even then the fraction in the complex is only a small part of that free in solution.

2. Dependence on other substances in solution

The addition of any one of a large number of organic acids to a solution of the protein-dye complex will reverse the effect of the protein on the spectrum. This reversal has been observed with each of the dyes investigated and is illustrated for orange I and azosulfathiazole in figures 16 and 17. Apparently the organic acid displaces the dye from its protein complex. The carboxyl ion and the sulfonate ion thus must compete for the points of attachment on the protein molecule.

A survey of the competitive abilities of a number of organic acids against azosulfathiazole is summarized in table 5. The reversing effect has been expressed in terms of $\Delta\epsilon$, the increase in extinction coefficient of the dye in an albumin solution containing the organic acid over that observed with only albumin and dye. From the data listed in this table it is quite clear that optical deviations depend not only on the nature of the protein but also on the nature of the buffer.

TABLE 5

Competition between acids and azosulfathiazole (5)

COMPOUND	CONCENTRATION	pH	$\Delta\epsilon$ AT MAXIMA	PER CENT COMPOUNI FORM OF ANION
	moles/liter			
p-Chlorobenzoic acid	1.18×10^{-2}	6.51	5100	100
o-Chlorobenzoic acid	1.18	6.51	4500	100
o-Aminobenzoic acid	1.35	6.45	4500	97
p-Aminobenzoic acid	1.34	6.45	2000	97
	1.44	9.02	0	100
Sulfanilic acid	0.96	6.55	1400	100
Sulfanilamide	1.31	5.12	0	0
Sulfamic acid	2.06	8.81	0	100
Salicylic acid	1.47	8.98	3100	100
Potassium acid phthalate	1.98	4.79	4300	75 A^-, 24 A^-
	0.49	5.42	3700	41 A^-, 59 A^-
	0.38	9.02	400	100 A^{--}
Maleic acid	1.60	5.82	3000	64 A^-, 36 A^-
	1.65	8.64	200	100 A^{--}
Succinic acid	1.71	4.38	0	58 A^-, 5 A^-
	1.65	8.72	0	100 A^{--}
Veronal	1.12	5.12	0	0

Thus phthalate buffers would reduce the protein errors very appreciably, particularly at low pH's. Similarly, if an organic metabolite is present in a medium of biological importance, the optical shifts due to the presence of protein may be quite different from those observed in the absence of the organic compound.

3. Dependence on pH

In the case of azosulfathiazole, the difference in heights of the absorption peaks in the absence and presence of albumin did not vary significantly over a pH range of 5 to 9. No studies could be made at higher pH's, since the interpretation of spectral changes in this dye is complicated by the ionization of the phenolic hydroxyl group.

With methyl orange, however, investigations can be made beyond pH 9 and lead to the striking results illustrated in figure 21. Clearly there is a decrease in the optical deviation due to the presence of protein as the pH is increased, with complete disappearance of any effect at pH's slightly above 11. Such behavior suggests that binding by the protein disappears at high pH's. This prediction has been confirmed by ultrafiltration[4] studies. Methyl orange is not bound by bovine albumin to any significant extent at pH's approaching 12.

It is also of interest to note that the reversing ability of a given carboxylic acid decreases with increase in pH. The trend is quite clear from the data in table 5 on potassium acid phthalate, *p*-aminobenzoic acid, and maleic acid, respectively. The decrease in affinity at high pH must be an expression of the increasing electrostatic repulsion of the organic ion, due to the increasing negative charge on the protein molecule.

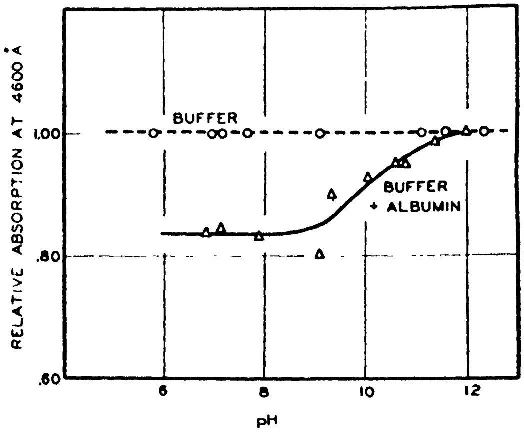


FIG. 21. Effect of pH on absorption spectra of methyl orange in albumin solutions

E. Nature of the protein-anion bond

The strength of the protein-anion bond, or the value of the intrinsic binding constant, K, seems to be determined by two factors, an electrostatic attraction and van der Waals interactions. The basis of an electrostatic attraction becomes evident if one considers the amino acid composition of a protein such as serum albumin. A very abbreviated schematic diagram of the structure of a protein is indicated in figure 22. At a pH of about 6, the basic amino acids, histidine, lysine, and arginine, are combined with a hydrogen ion and hence have a net positive charge, whereas the acidic amino acids, such as glutamic acid, have released a hydrogen ion and formed carboxylate ions. Since the isoelectric point of serum albumin is near pH 5, the number of carboxylate ions at pH 6 exceeds the number of quaternary nitrogen atoms and hence the net charge on the protein molecule is negative. Nevertheless, the presence of positively charged nitrogen atoms forms a focus of attachment for the negative sulfonate or carboxylate substituents of the dyes and small organic anions. A similar picture has been drawn to interpret the interactions of detergents with proteins (10, 15).

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[4] The dialysis-distribution method was avoided because the time required for equilibrium (72 hr.) may be sufficient to cause extensive denaturation of the protein at high pH's.

In the case of the dye-protein combinations described here, the electrostatic interactions seem to involve largely the lysine group of the protein. For on the basis of the picture outlined one would expect the binding to disappear at pH's where the quaternary nitrogen atoms lose their hydrogen ions and hence their positive charge. These pH's are listed in table 6. The region of transition in figure 21 corresponds rather well to the region in which the ε-ammonium group of lysine loses its hydrogen ion.

It is also evident from the experiments described that electrostatic interactions alone will not account for the relative behavior of different dyes and organic anions in combining with proteins. Thus, for example, the intrinsic affinity constant for azosulfathiazole (XI) and bovine albumin is greater than that for methyl orange (II) by an amount corresponding to over 500 cal. in ΔF^0. Since only one sulfonate group seems to be involved in the binding in each case, the additional intrinsic affinity which the protein has for azosulfathiazole must be attributed to the additional groups in this molecule. Since there are many added substituents it is impossible to single out one as most important, although it does seem likely that the van der Waals interaction of the added aromatic ring contributes the major portion of the extra stabilization energy.

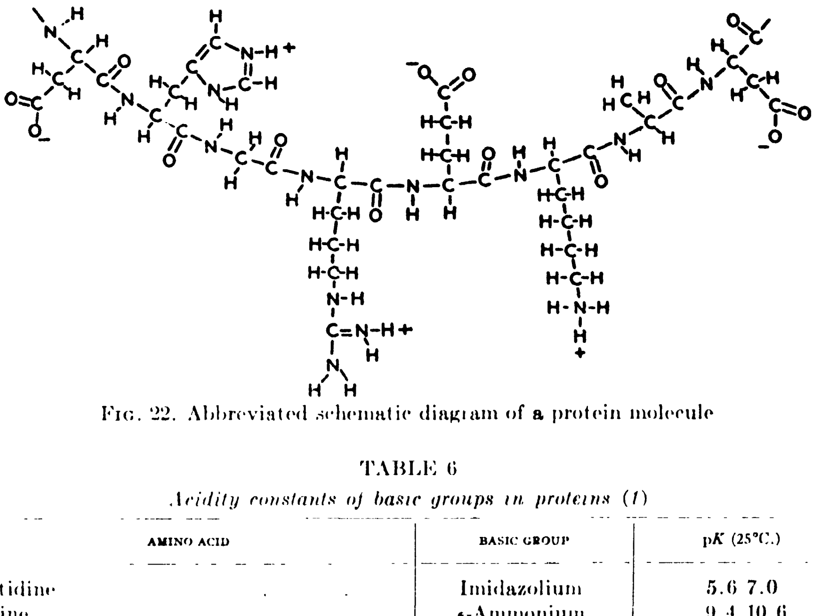

FIG. 22. Abbreviated schematic diagram of a protein molecule

TABLE 6

Acidity constants of basic groups in proteins (1)

AMINO ACID	BASIC GROUP	p*K* (25°C.)
Histidine	Imidazolium	5.6 7.0
Lysine	ε-Ammonium	9.4 10.6
Arginine	Guanidinium	11.6 12.6

Similarly, in the competition of small molecules with large dyes for binding positions on the protein it is evident that increasing pH puts the small molecules at a greater disadvantage. Apparently van der Waals forces contribute more to the stability of the protein-dye complexes than to that of the organic anion complexes, since the latter have at most but one aromatic ring. Hence at high pH's electrostatic repulsion is more effective against the organic anions than against the dyes, and therefore the competing ability of the former decreases.

Competition phenomena also show that van der Waals interactions alone are insufficient to maintain a stable bond in the complex. This seems evident from the fact that the undissociated organic acid is much less effective as a displacing agent than is the anion.

IV. CONCLUSIONS

The results of the investigations described here indicate that the effects of salts or proteins on indicator and dye spectra can be accounted for largely in terms of electrostatic interactions. These interactions may be of the Debye-Hückel ion-cloud type or may involve actual complex formation, as in the case of proteins. Where such interactions can be separated from other effects, the experimental data may be accounted for quantitatively by thermodynamic methods with the aid of the fundamental theory of electrostatics. For both salts and proteins, however, certain specific interactions are also encountered. For electrolytes, these effects may be visualized as ion-dipole interactions with the solvent molecules. In the case of the proteins, specificity phenomena must be related to the internal structure of these large molecules. The emphasis in these spectral studies is shifting, therefore, from the dye to the electrolyte and to the proteins, for these investigations offer another method of probing into the nature of these substances in aqueous solution.

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PHOSPHORESCENCE AND THE RÔLE OF THE TRIPLET STATE IN THE ELECTRONIC EXCITATION OF COMPLEX MOLECULES[1]

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The purpose of this paper is to present a discussion of the researches of Professor Gilbert N. Lewis and his associates which led to the identification of the phosphorescent state with the lowest triplet state of a complex molecule.[3] However, this paper does not consist of a review of all of the details of these researches. It is more in the nature of a commentary, and as such may be regarded as a supplement to the four basic papers on phosphorescence published by Lewis and his coworkers (13, 15, 16, 18). In addition to presenting highlights of previously published work, and new work reported at this Symposium, an additional section on the mechanism of excitation of the triplet state of complex molecules has been added. It may be remarked that the point of view adopted in this paper is that, since metastability of electronic levels may be due to various causes, a phosphorescent state may not be identified as a triplet state until definite physical evidence for this identification has been obtained.

I DEFINITION OF LUMINESCENCES OF COMPLEX MOLECULES

When the total luminescence of a complex molecule, in solution in a rigid glassy medium, is excited by high-frequency ultraviolet light and recorded spectrographically, it is found that, in general, only two distinguishable luminescences are observed. The luminescence of higher frequency is readily identified, by its spectral position and (short) mean emission lifetime,[4] as the reverse of the lowest-energy normal absorption process. On the other hand, the second luminescence occurs some 2000 cm.$^{-1}$ to 20,000 cm.$^{-1}$ below the normal absorption band and has a relatively long mean lifetime. Thus, it is usually observable with a low-speed phosphoroscope (rotating alternate vane shutter). The spectroscopic (15, 16) and magnetic (13, 14) studies of the metastable excited state giving rise to this long-lived luminescence have led to the conclusion that, in many cases, this metastable state is the lowest triplet state of the molecule.

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[3] The present discussion deals with the case of molecules having singlet ground states, which includes most of the complex molecules.

Several explanations for the long mean lifetime of phosphorescence of complex molecules (in rigid glasses) had been given previously. The apparent requirement of rigidity of the medium led to the geometrical isomer theory of phosphorescence.[5] A related idea consisted of the interpretation of the phosphorescent state as a tautomer of the normal molecule (6, 7), the return to the normal form being inhibited by the forces present in the rigid medium. However, as indicated in Section II, rigidity is not the fundamental requirement for the manifestation of phosphorescence. The requirements of the *triplet-state theory* of phosphorescence include several general points. According to this theory (15): (*a*) the long lifetime is to be ascribed chiefly to operation of the intercombination[6] selection rule, (*b*) the quasi-forbidden absorption from the ground to the phosphorescent state should be observable for cases having favorable mean phosphorescence lifetimes, and (*c*) the phosphorescent state should be paramagnetic. Each of these topics will be discussed in a later section of this paper.

Both the normal and the low-frequency luminescences are in many cases of such short duration that it is not possible to differentiate between them by the eye on the basis of mean lifetime. For this reason, and because of a belief in the generality of the triplet-state theory, it was proposed (15) that (in the field of complex molecule luminescences) the term *fluorescence* be applied to emissions involving no change in multiplicity, and the term *phosphorescence* be applied to emissions involving a transition between electronic states of dissimilar multiplicity.

In the special case of dyes, for which the normal-excited, and metastable electronic levels are separated by only 1500 to 3000 cm.$^{-1}$, thermal activation may lift molecules from the metastable to the unstable level, resulting in an emission spectrally identical with normal fluorescence, but having a relatively long mean lifetime. This emission has been named alpha-phosphorescence to distinguish it from spontaneous metastable-to-ground emission, which was named beta-phosphorescence (18). This mechanism of luminescence of dyes follows the interpretation made by Jablonski (10).

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[4] Time required for the emitted light to fall to $1/e$ of its intensity.

[5] This was discussed by Lewis, Lipkin, and Magel (18), together with the triplet-state theory of phosphorescence. See also Terenin (35).

[6] *Intercombination* refers to the process of combining (undergoing transition between) two electronic states of dissimilar multiplicity. *Intersystem* refers to general interrelations between states of dissimilar multiplicity.

However, metastability of an electronic level may be due to other causes than that of the simple operation of the singlet–triplet selection rule. Consequently, any absorption bands of relatively low intensity may have corresponding luminescences of relatively long mean lifetime. One example of such a low-intensity absorption is the case of the characteristic long-wave-length absorption band of carbonyl compounds. This absorption has been interpreted as corresponding to a transition in which a loosely bound electron, occupying a non-bonding orbital lying in the molecular plane and across the C—O direction, is excited to an excited molecular orbital with a node in this plane (McMurry (24)). Another example is the well-known low-intensity long-wave-length absorption band of benzene and certain substituted benzenes, for which the electronic transition is forbidden on symmetry grounds, as interpreted by Sklar, Sponer, *et al.* (8, 29, 30, 31, 33).

In some cases the long-lived luminescence may be ascribed to a triplet–singlet transition if it can be distinguished from other forbidden transitions which are possible. This may sometimes be done by its spectral position, or by a comparison of its mean lifetime with that calculated from the integrated absorption of the processes in question. In the final decision, only studies based on the paramagnetic nature of the triplet state can give an unambiguous assignment as a triplet–singlet emission. This is discussed more fully in Section X.

II. DEFINITION OF EXPERIMENTAL CONDITIONS

The literature on the luminescence of organic molecules in rigid media is sometimes complicated by failure to distinguish between emission spectra of the original molecule and species formed from it, such as various ionic forms, dimers, and higher polymers, and photochemical products produced during the illumination. Further, often no distinction is made between various physical states, such as dissolved, adsorbed, colloidal, or crystalline, in either crystalline or vitreous media. These factors often have a large influence on the optical properties of the molecule. This paper deals only with the case of dilute solution of the substance studied, in the form of homogeneous, transparent, rigid glassy media. Under such conditions it has been found that the luminescences observed are characteristic of the dissolved substance and not of the medium employed (15).

Thus, phosphorescence spectra of carbazole, in rigid glasses of dextrose (293°K.), glycerol (193°K.), and EPA (5 ether, 5 isopentane, 2 ethanol, by volume) (90°K.), were studied. These showed but relatively small differences in frequency of the highest-energy emission band and in the main vibration intervals (15). Similar experiments have been done at one temperature by Mr. R. V. Nauman of this Laboratory, in which the phosphorescence spectra were obtained for several substances in a variety of solvents, each supercooled to a rigid glassy state by means of a liquid-nitrogen bath (77°K.). The solvents used include various hydroxylic and hydrocarbon solvent mixtures, concentrated phosphoric acid, and concentrated sulfuric acid. It was found that the spectral characteristics of the phosphorescences were relatively little affected (20). A study of the vibrational structure of the phosphorescence spectra has shown that the vibrations are characteristic of the ground state of the molecule (15, 19, 25, 27).

Furthermore, it has been found that rigid media are not always essential for the observation of phosphorescence. Thus, the phosphorescence of a number of substances has been observed in glycerol solution at room temperature (2, 20). Similarly, the gas-phase luminescence of several substances was shown (16) to be nearly identical, in spectrum and mean lifetime, with the phosphorescence observed in rigid glasses at 77°K. Phosphorescence in fluid media is readily observed if the mean lifetime is intrinsically short, of the order of 10^{-3} sec. Substances having mean phosphorescence lifetimes of several seconds do not exhibit the phenomenon in fluid media at room temperature. From these facts it has been concluded (16) that the chief function of the rigid medium is to prevent viscosity-dependent quenching of the energy of the molecule in the metastable state. Quantitative experiments on the quantum yield of phosphorescence as a function of mean lifetime and viscosity would be very desirable.

Considering the respective rôles of the complex molecule and the rigid glassy medium in making up a complex molecule *phosphor* system, there is evidently no close analogy to the "activator" of mineral phosphor systems. The application of the term "activator" to the former system must be regarded as inaccurate and misleading.

III. PHOSPHORESCENCE OF NON-HYDROGENIC CARBON COMPOUNDS

Since it had been suggested that the phosphorescent state may correspond to a tautomer of the normal molecule (6, 7), it was of interest to investigate the phosphorescence properties of a number of molecules not containing hydrogen. The phosphorescences of a series of perchlorinated molecules were studied in rigid media (EPA, Section II) at 77°K. Data obtained for several different structural types are given in table 1. The lifetimes were estimated roughly by visual observation and are probably too long.

The data of table 1 show that even for molecules which contain no hydrogen atoms, phosphorescence of normal characteristics occurs. This of course would not be possible if normal tautomerism were operative in excitation of the phosphorescent state, in view of the absence of hydrogen in these molecules. It is possible that if very high vibrational levels were involved, resulting in a vibrationally energy-rich molecule, "tautomerism" of an abnormal nature might occur, causing a "shift" of very heavy atoms, such as would not ordinarily be expected (5). That is to say, in a highly vibrating state, a heavy atom may attain such a large displacement as to require merely a redistribution of bonds for its effectual transfer from one part of the molecule to another. However, as Professor M. Calvin has pointed out to the author, if such a "tautomerism" did occur, no mechanism would be available to explain the *spontaneous* return from the phosphorescent state to the normal state. In the emission process the molecule starts from the zero-point vibration level of the upper state, under the usual conditions of observation.

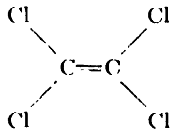
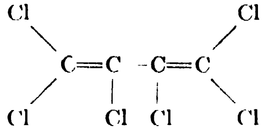
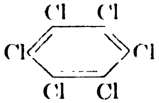
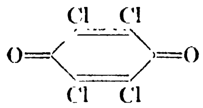
It is concluded that tautomerism does not play a fundamental rôle in phosphorescence phenomena in the case of most complex molecules.

IV. PHYSICAL CHARACTERISTICS OF (BETA) PHOSPHORESCENCE

In the case of mineral phosphor systems some evidence has been obtained for the occurrence of electron transfer during the excitation and emission processes. The independent study of electron transfer caused by illumination (by high-frequency ultraviolet light) of complex molecules in rigid glassy media (12, 17) has indicated that in the phosphorescence process in this system electron transfer is definitely not involved, as previously discussed (15).

TABLE 1

Phosphorescence characteristics of non-hydrogenic carbon compounds

COMPOUND	$\bar{\nu}_P$	APPROXIMATE MEAN LIFETIME
	cm.$^{-1}$	*sec.*
	26,000	2
	25,800	3
	24,170	0.1
	21,750	0.5

The observation of a strictly exponential decay law of phosphorescence of complex molecules, during normal time intervals (18, 22, 28, 36), is compatible with the idea of a spontaneous (unimolecular) emission. For time intervals which are long compared with the mean phosphorescence lifetime, involving a thousandfold variation in intensity of phosphorescence, it was found recently by Sveshnikov (34) that a noticeable deviation from the exponential decay law (phosphorescence of acid fluorescein dye) occurs. Also, there was found a slight dependence of the decay constant on the intensity of the exciting light.

Both these anomalies are in the direction of increased rate of decay during the existence of a higher concentration of molecules in the phosphorescent state. Professor M. Calvin has pointed out to the author that these deviations may be due to a magnetic quenching resulting from the interaction of a molecule in the triplet state with the inhomogeneous magnetic fields produced by neighboring triplet-state molecules (see Section V). As the phosphorescence decays, the influence of the fields would diminish and the quenching would decrease, as observed.[7]

Finally, three other physical characteristics of phosphorescence which have been studied deserve mention. (*a*) Beta-phosphorescence has been found to be nearly temperature-independent (18), while alpha-phosphorescence is strongly temperature-dependent, as pointed out in Section I. (*b*) Beta-phosphorescence shows very little polarization (18, 26), while alpha-phosphorescence is polarized similarly to normal fluorescence. (*c*) Wide-angle interference-pattern studies of the phosphorescence of acid fluorescein dye, by Weissman and Lipkin (38), have demonstrated that the electromagnetic radiation mechanism is *electric dipole* emission.

V. PARAMAGNETISM OF THE PHOSPHORESCENT STATE[8]

That the phosphorescent state is paramagnetic in certain cases was first demonstrated by Lewis and Calvin (13). A direct measurement of the paramagnetism of the phosphorescent state is possible in the case of complex molecules because of the phosphorescence saturation phenomenon (18) arising from the long mean lifetime (seconds), whereby a large fraction of the molecules may be held in the phosphorescent state by illumination of the phosphor with an intense light source. The experiments of Lewis and Calvin were performed on the phosphorescent state of acid fluorescein dye, using a Theorell horizontal microbalance. Later experiments (14) permitted a quantitative determination of the value for the molal paramagnetic susceptibility, the results of which are given here.

For acid fluorescein dye in the 2.5-sec. phosphorescent state in boric acid glass at room temperature, a steady-state concentration of 3.23×10^{-8} moles per centimeter length produced a boom displacement of 4.43×10^{-3} cm., corresponding to a pull of 1.17×10^{-2} dynes. These data yielded a value of 2100×10^{-6} C.G.S. units for the molal paramagnetic susceptibility of the phosphorescent-state molecules. This value is about two-thirds of the value given for the triplet state of oxygen at the same temperature. The discrepancy is attributed to the thermal depopulation of the phosphorescent state (as described in Section I) due to warming of the sample by the high-intensity exciting source. Owing to this discrepancy the experiments are being repeated at low temperatures; a full report on this research is postponed until a later date.

VI. MEAN LIFETIME OF THE PHOSPHORESCENT STATE

For the triplet-state theory of phosphorescence to be valid, it is important to establish the fact that the range of observed mean lifetimes is consistent with the transition probability expected theoretically for a triplet–singlet emission.

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[7] The effects observed by Sveshnikov could be due to warming of the sample by the high-intensity light, although it seems unlikely that the boric acid glass would cool sufficiently during the decay time to influence the decay constant.

[8] Reported at this Symposium by Professor Melvin Calvin.

Lifetimes roughly estimated by visual observation (15) indicated a range of about 10^{-4} to 50 sec., with a strong dependence on molecular structure. More recent quantitative measurements indicate that the visual estimates were somewhat long in most cases. Since the careful experimental and theoretical study of the problem of phosphorescence lifetimes of complex molecules is under way at this Laboratory (23), further discussion will not be given here. For atomic cases the quantum-mechanical treatment of intensities of singlet–triplet transitions relative to singlet–singlet transitions is well known. It is interesting that approximations for the corresponding processes in complex molecules, based on a model using atomic wave functions and assuming spin–orbit coupling, give triplet–singlet lifetimes which are of the same order of magnitude as observed phosphorescence lifetimes (1).

VII. CHANGE OF CONFIGURATION IN EXCITATION OF THE TRIPLET STATE

The excitation of a non-dissociated low-energy triplet state of a complex molecule requires the uncoupling of the spins of a pair of unsaturation electrons. The resultant triplet state may then be considered as analogous to a diradical. Thus, it is apparent that in excitation to the triplet state the configuration of the complex molecule may be affected in a direct way. It has been found interesting to attempt to construct a model for the most probable diradical configuration of the triplet state of various types of molecules in terms of classical chemical structures[9] (15).

The study of phosphorescence characteristics (15) (energy of the phosphorescent state above the ground state, as determined by highest-frequency emission band; mean lifetime of emission; vibration pattern) showed that within certain molecular types essentially similar characteristics occurred. Thus, for derivatives of an aromatic ring molecule (substituted by such saturated groups as alkyl, alkoxy, halogen), closely similar phosphorescences are obtained. For example, most benzene derivatives (20) have phosphorescent-state energies of about 80 kcal., naphthalene derivatives about 60 kcal.; and the mean emission lifetimes are in the range 5–10 sec. and 1–4 sec., respectively (23). Both benzene derivatives and naphthalene derivatives have many-banded phosphorescence spectra of sharp fine structure.

On the other hand, when a series of aromatic nitro compounds is studied, it is found that the phosphorescence characteristics are very different from those of the parent molecule, and in fact quite consistent regardless of the aromatic nucleus. Thus, most aromatic nitro compounds (e.g., nitronaphthalenes, nitrofluorenes, nitrobiphenyls) have phosphorescent-state energies of about 57 kcal., mean lifetimes of about 0.1 sec., and a characteristic spectrum consisting of an evenly spaced (in frequency) set of diffuse emission bands. Analogously, many aromatic ketones have been found to have mean phosphorescence lifetimes of about 10^{-3} sec., also with a characteristic spacing of diffuse emission bands. In this case however, the energy of the phosphorescent state varies widely, depending on the ketone, presumably owing to electronic interaction of the carbonyl group with the rest of the molecule.

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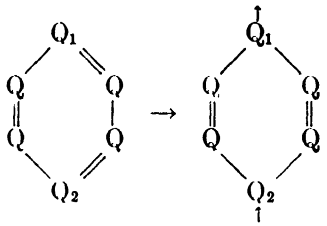
[9] The procedure of assigning energy increments for the factors contributing to the energy of the triplet state, as used in the earlier work on phosphorescence, will be omitted from the present discussions, owing to its somewhat arbitrary nature.

The consideration of such phosphorescence data led to the idea that the excitation of the triplet state involved essentially different molecular mechanisms in each structural type. Thus, in some cases the excitation could be considered as confined to a diatomic double-bonded array, involving a localized molecular orbital, pictured as follows:

$$Q_1{=}Q_2 \rightarrow \overset{\uparrow}{Q_1}{-}\overset{\uparrow}{Q_2}$$

where each Q represents an atom, one or both of which may be bonded to other atoms; the small arrows represent the parallel-spin electrons which give rise to the triplet multiplicity. There would be a characteristic change in interatomic distance expected for such an excitation. In the case of excitation of a cyclic structure, the configurational change may be pictured thus:



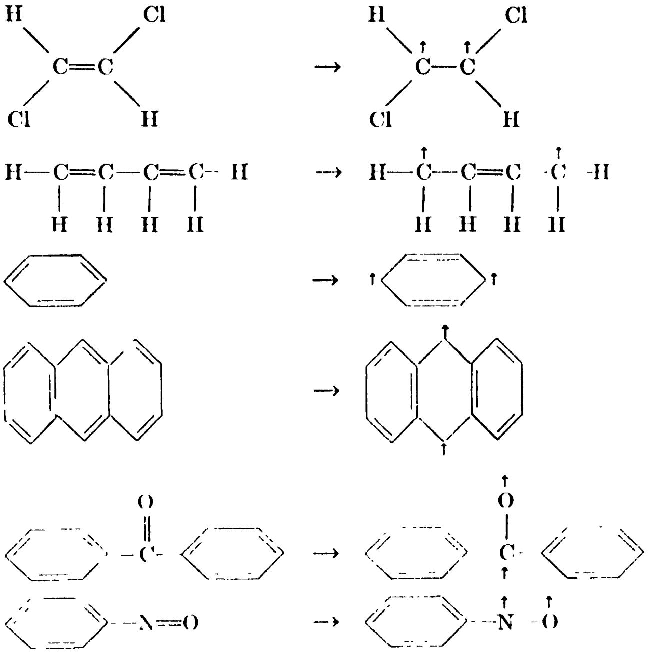
in which case the net displacement of Q_1 and Q_2 would be less than for the diatomic array (on the basis of classical structures and normal bond distances and angles). When the electrostatic repulsion of the two electrons is considered, it may be expected that (*a*) if confined to a diatomic array, the repulsion would further increase the interatomic distance for the diradical configuration, or (*b*) if the geometry of the molecule permitted, the electrons would tend to separate, e.g., favoring para positions in the above case to ortho positions.

Table 2 illustrates the postulated configurational changes for triplet-state excitation of several actual molecules. Various alternative structures would have to be considered for a more accurate picture. In such a case as benzophenone, the decision as to whether the benzene ring or the carbonyl group is the principal locus of excitation is made on the basis of phosphorescence characteristics alone. In most cases an unambiguous differentiation may be made, by comparison with the characteristics obtained for the two competing parts of the molecule when studied separately (i.e., linked to electronically inert groups). It may be pointed out that in the case of benzene the *p*-quinoid model for the triplet state is supported by the intensity relations of the phosphorescence emission spectrum (15), and by a vibrational analysis of the fine structure of the spectrum (27).

This picture of triplet-state excitation is of course very crude, but, subject to certain refinements, it does give an interpretation of the variation in phosphorescence characteristics enumerated above. Use of this model has facilitated the development of the picture of mechanism of excitation of the phosphorescent state, discussed in Section VIII of this paper. Furthermore, the model may be used to explain certain permanent changes occurring in some photochemical reactions, such as photoisomerization about a double bond. A triplet state intermediate in a number of such photochemical processes is suggested.

TABLE 2

Postulated change of molecular configuration in excitation of the triplet state



VIII. MECHANISM OF EXCITATION OF THE TRIPLET STATE

The mechanism of excitation of the phosphorescent state deserves special consideration. Let the discussion be limited at first to the cases in which the phosphorescent state is a triplet state. Excitation of this state as a result of direct transition from the ground state by light absorption may be expected to occur but rarely, i.e., with very low probability (see Section X). Thus, excitation of the triplet state must almost always involve primary absorption to one of the excited singlet states. The ratio of the mean lifetimes of normal fluorescence $({}^1\Gamma^* \rightarrow {}^1\Gamma)$ (excited singlet → singlet)[10] and phosphorescence $({}^3\Gamma \rightarrow {}^1\Gamma)$ (defined

[10] *Nomenclature*: In the papers of Lewis and Kasha (15, 16) singlet states were designated by S, S', S'' and triplet states by T, T', T''. In this paper these are replaced by ${}^1\Gamma$, ${}^1\Gamma^*$, ${}^1\Gamma^{**}$ and ${}^3\Gamma$, ${}^3\Gamma^*$, ${}^3\Gamma^{**}$, in conformity with usual spectroscopic practice. Γ is an arbitrary term symbol, and the asterisks indicate simply that the states are different, but more than this is not known. $\Gamma \leftarrow \Gamma$ denotes absorption and $\Gamma \rightarrow \Gamma$ denotes emission, with the state of highest energy placed first in order.

in accordance with the limitation given above) is on the order of 10^{-8} to 1 sec., respectively. Therefore it is obvious that, assuming similar intercombination transition probabilities, the $^1\Gamma^* \rightarrow {}^3\Gamma$ process cannot be a radiative one (see figure 2). It was formerly postulated (6, 7, 18) that in the excitation of the phosphorescent state the molecule in the $^1\Gamma^*$ state is first transferred, by an internal conversion of energy, to a high vibrational level of the $^1\Gamma$ state. Then transfer to the phosphorescent state could occur when a favorable configuration was acquired, while slowly (it was assumed) falling through the $^1\Gamma$ vibrational levels in the neighborhood of the phosphorescent state.

An analysis of the details of the processes involved in normal absorption and emission of light indicates that the mechanism described above cannot be valid. Studies of the absorption spectra of complex molecules in rigid glasses at low temperatures indicate that the vibrational cascade to the zero-point level of the $^1\Gamma^*$ state, after primary absorption has occurred, is very rapid compared with the mean lifetime of the $^1\Gamma^*$ state. It may then be expected that vibrational cascade through the levels of the $^1\Gamma$ state would be just as rapid as it is in the $^1\Gamma^*$ state. Thus the mechanism of excitation of the phosphorescent state could not depend on a slow passage through the $^1\Gamma$ vibrational levels, even in a rigid medium. During the process of primary absorption the molecule remains longest at, or slightly above, the zero-point level of the $^1\Gamma^*$ state before normal fluorescence ($^1\Gamma^* \rightarrow {}^1\Gamma$) occurs. Hence it is logical to assume that the radiationless internal conversion ($^1\Gamma^* \rightarrow {}^3\Gamma$) will occur with maximum probability *at or above* the zero-point level of the $^1\Gamma^*$ state.

By the use of a schematic potential-curve diagram (figure 1) instead of the line energy-level diagram (figure 2), a more accurate picture of the place of interaction (on the energy diagram) may be obtained. The mechanism of excitation of the triplet state, according to this picture, involves an intersystem "crossing" of potential curves for the $^1\Gamma^*$ and $^3\Gamma$ states. The mechanism sequence may be outlined as follows: primary absorption of light ($^1\Gamma^* \leftarrow {}^1\Gamma$), rapid vibrational cascade to the vicinity of the zero-point level of the $^1\Gamma^*$ state, with simultaneous intersystem crossing ($^1\Gamma^* \rightarrow {}^3\Gamma$), followed by vibrational cascade to the zero-point level of the $^3\Gamma$ state. Thereafter, spontaneous phosphorescence emission ($^3\Gamma \rightarrow {}^1\Gamma$) may occur. A detailed consideration of the factors involved leads to the conclusion that if the crossing of the potential curves occurs at the lowest point of the $^1\Gamma^*$ curve, the probability of internal conversion will be greater than for cases in which crossing at a higher point of the $^1\Gamma^*$ curve occurs.

For a complex molecule such a diagram requires a special definition of coördinates, since for such molecules a potential hypersurface would be required to show the dependence of electronic energy on the configuration for each electronic state. Here a simplification may be introduced, based on the model for triplet-state excitation presented in Section VII. A critical coördinate is first selected, corresponding to the principal axis of excitation of the triplet-state configuration. Then the schematic potential curves may be interpreted as representing time-average cross-sections of the potential-energy hypersurfaces for the electronic states along this critical coördinate. From the model it may be assumed that the $^3\Gamma$ minimum will come at larger values of interatomic distance than the minima of the $^1\Gamma^*$ and $^1\Gamma$ potential curves.

After the internal conversion to the $^3\Gamma$ state (n^{th} vibrational level) has occurred, the $^1\Gamma^* - {}^3\Gamma$ energy difference (A of table 3, Section IX) must be dissipated as vibrational energy of the $^3\Gamma$ state. This energy is often about 20-30 kcal. per mole, and although considerable, it is not of an astronomical order of magnitude compared with the 5-10 kcal. per mole which must be dissipated in the $^1\Gamma^*$ state each time that normal absorption to high vibrational quanta occurs in a complex molecule. Furthermore, in a rigid glassy medium at low temperatures, cascade by infrared radiation may become probable, as may infrared transmission by the medium, thus facilitating removal of the excess energy from the immediate neighborhood of the molecule.

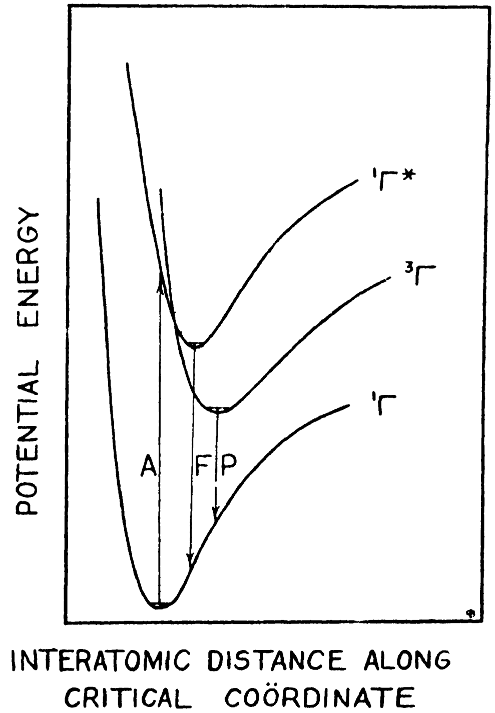


FIG. 1. Schematic potential-energy diagram of the three lowest electronic states of a complex molecule, depicting potential hypersurface cross-sections along a critical coördinate. After primary absorption, fluorescence may occur, and in addition, radiationless intersystem-crossing followed by phosphorescence.

Several interpretations of luminescence phenomena on the basis of crossing of potential curves have been made previously (3, 4, 5a, 37), but these have involved only two electronic states, or repulsive third states, and a more arbitrary definition of coördinates than is given here. From the non-destruction of the normal molecule upon repeated cycles of absorption and phosphorescence emission, it is concluded that dissociation does not occur in the excitation of the phosphorescence of complex molecules.

Throughout this section, the triplet-state theory of phosphorescence has been assumed because of the requirements imposed by the definitions of coördinates. Other metastable states may have a similar mechanism of excitation. A full discussion of this mechanism and its consequences in the optical behavior of complex molecules will be given shortly in another place by the author, together with experimental work supporting the mechanism pictured. One of the consequences of this treatment has been an interpretation of the lack of correlation (5) between the spectroscopic and thermal energy differences between the $^1\Gamma^*$ and $^3\Gamma$ states of dye molecules (11), not expected on the basis of the Jablonski mechanism of luminescence (10).

IX. THE FLUORESCENCE–PHOSPHORESCENCE FREQUENCY INTERVAL

A compilation of fluorescence–phosphorescence frequency intervals for complex molecules, giving the difference between the highest frequency bands of the two luminescences, $\bar{\nu}_F - \bar{\nu}_P$, apparently has not been made hitherto. Nevertheless, this molecular constant is of considerable aid in interpreting luminescence phenomena. Table 3 gives some examples of such data which, while not extensive, are typical for each group of molecules given.

The last column of table 3 gives A, the $^1\Gamma^* - {}^3\Gamma$ zero-point energy interval in kilocalories per mole (assuming, tentatively, a triplet metastable state), which varies widely for different structural types. Within particular groups of molecules, however, this energy interval is fairly constant. Thus, most benzene derivatives (in which the substituents are saturated groups like alkyl, alkoxy, halogen) have values of A of 23 kcal.; naphthalene derivatives about 30 kcal.; amines roughly 15 kcal. This energy interval may be considered as depending chiefly on two factors: (*a*) the configuration change involved in the excitation of the triplet state (see Section VII), and (*b*) the difference in resonance energy between the $^1\Gamma^*$ and $^3\Gamma$ states.

It will be noted that, in contrast to the moderate constancy of the interval for the cases cited above, the aromatic hydrocarbon series benzene, naphthalene, anthracene, phenanthrene, chrysene, have respective $^1\Gamma^* - {}^3\Gamma$ energy intervals of 22.1, 34.5, 28.7, 20.3, 22.4 kcal., indicating a large variation in one or both of the two critical factors. In the case of dyes, the abnormally low $^1\Gamma^* - {}^1\Gamma$ (*normal absorption band*) energy interval brings the $^1\Gamma^*$ much closer to the $^3\Gamma$ state (which latter is not correspondingly lowered by the low-energy electronic processes of dyes; *cf.* figure 2), so that the $^1\Gamma^* - {}^1\Gamma$ interval is only 5–10 kcal. As indicated in an earlier section, this small value of A leads to luminescence phenomena peculiar to dye molecules.

The strikingly large values of A occurring for most other complex molecules have been somewhat overlooked in the past, possibly owing to a disproportionate interest in the luminescence properties of dyes. A full discussion of the importance of the energy interval A in the mechanism of excitation of the phosphorescent state will be given elsewhere by the author.

X. SINGLET–TRIPLET ABSORPTION BANDS OF COMPLEX MOLECULES

Since transition probabilities for the absorption and emission of light between two electronic states are related thermodynamically, the observed mean lifetime of the phosphorescent state may be compared with the lifetime calculated from the integrated absorption of an assumed reciprocal process. This was done in a broad way by Lewis and Kasha (16), who considered also the limitations of the classical transition probability equation relating intensities when applied to spectra of complex molecules. Although the quantitative correlations of intensities which could be made were limited in number, it was definitely established that the phosphorescence emissions studied were the reverse of the quasi-forbidden absorption bands considered.

TABLE 3

Fluorescence–phosphorescence frequency relations of complex molecules

COMPOUND	$\bar{\nu}_F$	$\bar{\nu}_P$	$\bar{\nu}_F - \bar{\nu}_P$	A
	cm.$^{-1}$	*cm.*$^{-1}$	*cm.*$^{-1}$	*kcal.*
Benzene	37,037	29,325	7,712	22.1
Naphthalene	33,300	21,300	12,033	34.5
Anthracene	24,700	14,700	10,000	28.7
Phenanthrene	28,818	21,740	7,078	20.3
Chrysene	27,800	20,000	7,810	22.4
Toluene	37,037	28,800	8,237	23.6
Ethylbenzene	37,037	28,950	8,087	23.4
n-Propylbenzene	37,037	28,900	8,137	23.3
Anisole	35,461	28,200	7,261	20.8
α-Fluoronaphthalene	31,900	21,100	10,800	30.9
β-Chloronaphthalene	31,900	21,100	10,800	30.9
α-Naphthol	31,400	20,500	10,900	31.2
β-Naphthol	30,550	21,100	9,450	27.1
β-Naphthonitrile	30,000	20,600	9,400	26.9
Aniline	32,051	26,800	5,251	15.5
Diphenylamine	31,670	25,200	6,470	18.5
Carbazole	29,100	21,500	4,600	13.2
Acid fluorescein	21,000	17,700	3,300	9.5
Crystal violet	15,700	13,500	2,150	6.2
Eosin (sodium salt)	16,950	14,900	2,050	5.9
Diisopropylbromonitrosomethane	>30,000	13,600	>16,400	>47.0

It is possible to establish the reciprocal nature of two transitions for a complex molecule by other means than intensity correlation. Thus, if the absorption and emission bands each involve a single electronic transition, a correlation of the highest frequency of emission with the lowest frequency of absorption would establish the correspondence. These frequencies may be expected to be equal except for a small dissipative energy loss, the magnitude of which may be estimated from the half-width of the individual bands. A single mean lifetime for the emission spectrum establishes the singleness of an electronic transition in emission, and a "mirror-image symmetry" (21; for examples see 9, 19) of the vibration envelope of the absorption spectrum may establish the singleness for the absorption process.

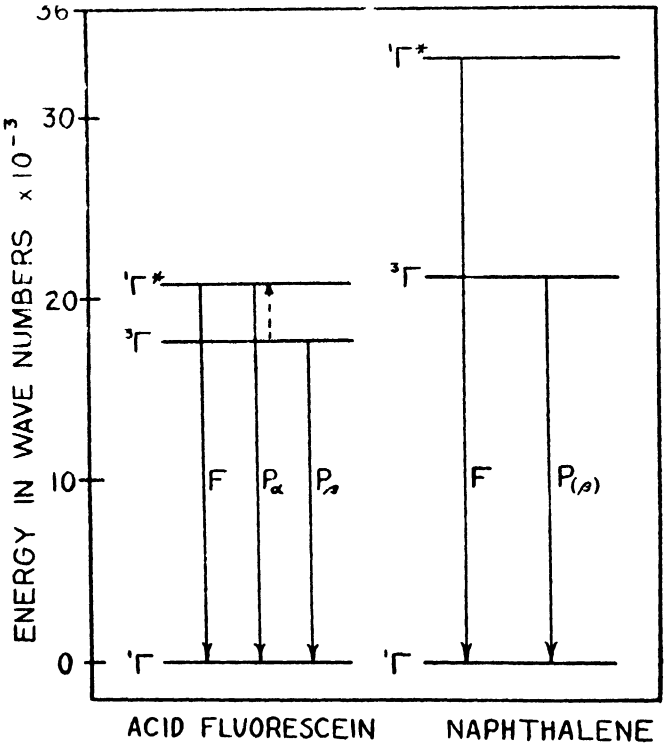


FIG. 2. Line energy-level diagrams for a typical dye and a typical complex molecule. Only the zero-point vibrational levels are shown, and the ground states are set equal arbitrarily. In the case of naphthalene the assignment of the triplet multiplicity to the lowest excited state is tentative. The $^1\Gamma^* \leftarrow {}^3\Gamma$ thermal activation is usually not observed in ordinary complex molecules at the temperatures available (< 298°K.), owing to the magnitude of this energy interval relative to kT.

Although the intensity and frequency correlations may prove the correspondence between absorption and emission processes, the correlation gives no direct information as to the *nature* of the electronic transition involved. The association of forbidden electronic transitions with a triplet-singlet process may be made in three ways: (*a*) by demonstration of the paramagnetic nature of the metastable state,[3] (*b*) by comparison with assignments of triplet levels on the basis of quantum-mechanical calculations, and (*c*) by elimination, when other known interpretations of forbidden transitions can be shown not to apply.

Method (*a*) is conclusive, but has been applied only in one case, the 2.5-sec.

state of acid fluorescein dye. Unfortunately, the long mean lifetime and intense normal color make observation of the forbidden absorption process impossible. This direct paramagnetic measurement method will prove very useful in many cases, and an extensive program of investigation based on it is being planned.

Method (*b*) has been applied to the phosphorescence spectrum of benzene (15), for which the highest-frequency emission band comes at $\bar{\nu}_P$ = 29,325 cm.$^{-1}$ (20), a value which corresponds to the weak absorption band at 29,400 cm.$^{-1}$ assigned as a $^3\Gamma \leftarrow {}^1\Gamma$ transition by Sklar (29) on the basis of quantum-mechanical calculations. The existence of this weak absorption band was corroborated by Lewis and Kasha (16), who found four maxima at 29,400, 30,300, 31,200, and 32,100 cm.$^{-1}$, with a molal absorption coefficient of $\epsilon = 0.0004$. It is interesting to note that in this case by two independent approaches—one the study of phosphorescence, and the other a quantum-mechanical treatment—the same low-intensity absorption band was tentatively assigned to a singlet–triplet transition.

Method (*c*) does not give an unambiguous identification of a forbidden transition as a singlet–triplet process, but it can give conclusive proof that a particular transition is not to be interpreted on the basis of a particular known cause of prohibition. This is well illustrated by the case of carbonyl compounds. The phosphorescence emission of many carbonyl compounds has been studied (15) and recently, accurate determination of the mean lifetimes of the phosphorescence state of these has been made (23). The emission spectra occur at frequencies a little below the characteristic long-wave-length carbonyl absorption band, for which an interpretation as a forbidden transition has been given by McMurry (24), as mentioned in Section I. However, the integrated absorption of this band predicts a mean lifetime about 100 times shorter than is observed; in other words, the carbonyl absorption is too intense by a factor of 100, for a complete identification with the long-lived (*ca.* 10^{-3} sec.) emission observed. Probably the absorption bands consist of two superposed forbidden electronic transitions. The occurrence of fine structure in the characteristic carbonyl band of some compounds suggests this to be the case, especially in the case of certain diketones (16).

Examples of known low-intensity absorption bands of complex molecules are given in table 4. It is not meant to be implied that these are all singlet-triplet bands; this table merely represents material for study as possible cases. In the case of thiobenzophenone a very good correlation between absorption and emission frequencies and mirror-image symmetry was obtained (16). The absorption coefficient as given is thought to be somewhat in error owing to an impurity of benzophenone, and the lifetime was not measured but only a lower limit established. Thus, an intensity correlation was not achieved, although it is important to do this, since McMurry (24) has suggested that his interpretation of the low-intensity carbonyl bands may apply also to thiocarbonyls. Because of its unique spectral position, it seems rather likely that the thiobenzophenone absorption band in the infrared represents a single electronic transition. A decision as to the cause of prohibition, that of intercombination or otherwise, would be of great interest. However, the suggestion made below offers some evidence for an intercombination process in this case.

In a number of instances, the low-intensity absorption bands observed for nitroso compounds have been correlated with phosphorescence emission spectra (16), though again only partly. Whether the bands are definitely singlet–triplet was not ascertained. It is of interest to point out that in many cases of thiocarbonyl and nitroso compounds the solid state is colorless, while the solutions are colored. More generally, the monomeric state is colored, while dimers and other polymers (which form readily with these compounds) are colorless. If two triplet molecules associated with intermolecular electron coupling, upon polymer formation or upon crystallization, the color would disappear if due to a singlet–triplet absorption in the monomer.

TABLE 4

Forbidden absorption bands of complex molecules

MOLECULE	COLOR	MOLAL ABSORPTION COEFFICIENT	ABSORPTION $\bar{\nu}$	EMISSION ν	$\int \epsilon \, d\bar{\nu}$	CALCULATED τ (ASSUMING $s = t$)	OBSERVED τ
			$cm.^{-1}$	cm^{-1}		*seconds*	*seconds*
1. Thiocarbonyl.							
Thiobenzophenone	Blue	3	16,000	13,800	9,300	2.3×10^{-4}	$<10^{-3}$
2. Carbonyl.							
Biacetyl	Yellow	22	22,500	19,700	77,500	1.16×10^{-5}	1.65×10^{-3}
Glyoxal	Yellow	3.5	21,700		9,660	1.17×10^{-4}	
3. Nitroso							
Nitrosodiethylaniline	Green	0.6	12,200		1,700	1.7×10^{-3}	
Isopropylbromonitrosomethane	Blue		14,560	13,600			
4. Azo:							
Diazomethane	Yellow	5	25,200		27,000	3.6×10^{-5}	
Azomethane	Yellow	1.6	29,500		27,000	2.6×10^{-6}	
5. Aromatic nuclei:							
Benzene		0.0001	29,400	29,325	~ 0.5	~ 1	1.0*
p-Dichlorobenzene			26,400	26,000			0.01*
Phenazine		0.8	(16,000)	15,300	620	2.8×10^{-3}	$<10^{-2}$

* Reference 23, unpublished work.

The low-intensity absorption bands listed for the two simple aliphatic azo compounds are also of interest for the present discussion, but luminescence studies of these have not yet been made. For a few aromatic hydrocarbons, extremely low-intensity absorption bands have been found. Like the case of benzene, an analogous though more obscure set of bands was obtained for p-dichlorobenzene. The frequencies matched very well, and the intensities roughly (a large experimental error in the integration is inevitable with such low absorption).

The aspect of luminescence research considered in this section is of great importance because of the elucidation of the nature of forbidden absorption bands of complex molecules which it promises to give. Faint colors, anomalous in normal color theory, may find their explanation in intersystem[6] transitions. The lack of data in table 4 emphasizes the need for thorough quantitative work on this subject.

In the last analysis the absolute assignment of a forbidden electronic transition, as a singlet-triplet process, will probably depend on the paramagnetism of the triplet state. Other methods than the direct measurement by microbalance are available. An attempt to determine the paramagnetism of molecules in the phosphorescent state by molecular-beam techniques is being made by Harrison Shull, working with Professor G. E. Gibson at this Laboratory. Also a number of indirect methods may be found useful, e.g., the effect of applied fields in the mean phosphorescence lifetime, either external fields or fields due to molecules in the environment of the excited molecule (see also end of Section XI). The availability of such a variety of methods should make it possible to apply at least one to each case of forbidden transition in question.

XI. ABSORPTION OF LIGHT BY MOLECULES IN THE PHOSPHORESCENT STATE

The phenomenon of phosphorescence saturation, which corresponds to the building up of a high concentration of molecules in the phosphorescent state, permits the study of the properties of this state as distinguished from those of the normal molecule. The study of the magnetic properties was described in Section V; the study of optical properties of the phosphorescent state is considered in this section.

Early in the work on the optical phenomena of complex molecules in rigid glasses, it was observed that in some cases a transient colored state was produced by intense illumination, decaying upon removal of the exciting light. This transient color, it was noted, is *color by absorption* and not luminescence, although both are present simultaneously and both decay with the same mean lifetime. It was recognized that this color is due to absorption from the ground metastable level to other electronic levels of the same type $({}^3\Gamma^* \leftarrow {}^3\Gamma, {}^3\Gamma^{**} \leftarrow {}^3\Gamma)$ (here a metastable triplet level again is assumed). As expected, the intensity of absorption varied with the intensity of the exciting light.

The absorption spectrum of the phosphorescent state of acid fluorescein dye was determined (18), although in this instance the color of the dye due to normal absorption masks the new absorption produced. However, the absorption spectrum of diphenylamine in the phosphorescent state was also determined (17), and in this case a transient violet color is observed upon intense illumination. It was shown that the color was not due to photochemical decomposition of the molecule.

It may be expected that ${}^3\Gamma^* \leftarrow {}^3\Gamma$ absorption bands should be quite generally observable with complex molecules having the longer-lived phosphorescent states. Perhaps the occurrence of such an absorption could be taken as evidence for the triplet multiplicity of a metastable state,[3] since it would be difficult to account for this absorption phenomenon in the case of some of the other causes of prohibition of electronic processes.

XII. CONCLUSION

The phosphorescence spectra of several hundred complex molecules have been recorded (15, 20). In the case of acid fluorescein dye, direct measurement of paramagnetism has established the fact that the phosphorescent state is a triplet state. Indirect (but not conclusive) evidence for this identification has been obtained for benzene ($\bar{\nu}_P$ = 29,325 cm.$^{-1}$), *p*-dichlorobenzene (26,000 cm.$^{-1}$), diphenylamine (25,200 cm.$^{-1}$), thiobenzophenone (14,100 cm.$^{-1}$), and several nitroso compounds. It is believed that the phosphorescence observed at about 2000 cm.$^{-1}$ to 20,000 cm.$^{-1}$ below the normal absorption band of a complex molecule will prove to be triplet–singlet transitions in most cases.

The phenomenon of the phosphorescence of complex molecules, and the use of rigid media, must therefore be looked upon as convenient means of observing forbidden electronic transitions in emission. Whereas the absorption process becomes increasingly more difficult to observe with increasing prohibition, the emission process becomes increasingly easy to observe, since greater prohibition corresponds simply to longer mean lifetimes of the excited state.

The identification of metastable electronic states as triplet states is of more than academic interest. In addition to offering an interpretation of some low-intensity absorption bands of complex molecules, often giving rise to anomalous color, the triplet state may be expected to be of great photochemical importance. The absence of long-lived luminescence in fluid media does not mean that excitation of the metastable state does not take place, but merely that this state is deactivated, owing to viscosity-dependent quenching.

When the metastable state is a triplet state, the fact that it is long lived, has a diradical configuration, and may be excited in fluid media at ordinary temperatures, suggests an important rôle for this state in photochemical processes in ordinary chemical systems.

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The most incalculable debt we owe to the late Professor Gilbert N. Lewis, for his visualization of the form of a broad theory with its implications at a time when luminescence was regarded as something of a curiosity, notwithstanding its extensive practical applications.

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THE HALOGEN FLUORIDES

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I. INTRODUCTION

The halogen fluorides make up the most reactive class of chemical compounds known, with some members of the group approaching elemental fluorine itself in reactivity. Under the proper conditions, they appear to react with all organic materials, with all of the metals, and with all of the non-metals excepting the inert gases and nitrogen and oxygen. They decompose water to give ozone and oxygenated halogen acids. They react with most salts to form the corresponding fluorides. They have been used in the preparation of organic fluorides and should find a wide variety of other applications where the action of elemental fluorine in a modified degree is desired.

In view of the recent commercial availability of some of the halogen fluorides, it seems particularly timely to assemble all the published information pertaining to them. These substances appear to offer such a wealth of possibilities for attacks on both theoretical and applied problems that a summary of the available information relating to them should prove useful.

II. IODINE PENTAFLUORIDE

A. PREPARATION

In a historical sense, the fluorides of iodine take precedence over the other members of the group. The possibility of the formation of a compound of fluorine and iodine was recognized as early as 1845 by H. B. Leeson (12). This investigator thought that he had prepared such a compound by passing the gas generated from one part of manganese dioxide, three parts of calcium fluoride, and six parts of concentrated sulfuric acid through water containing iodine until the whole of the iodine was taken up. Since both of the known iodine fluorides react with water, it appears that Leeson was mistaken.

Although he did not recognize it and reached an incorrect conclusion, Kammerer (7) was probably the first to prepare iodine pentafluoride. He heated dry silver fluoride and iodine together in a sealed tube to 70–80°C. After 24 hr. the color of iodine disappeared. The gaseous portion of the reaction product was collected over mercury and absorbed by aqueous potassium hydroxide. Since the resulting solution gave no test for the iodide ion, Kammerer erroneously concluded that he had isolated fluorine.

The actual nature of this reaction was clarified by Gore (3, 4, 5), who showed that iodine and silver fluoride under the influence of heat yield silver iodide and a fluoride of iodine. At 90–315°C. iodine reacts only slowly with silver fluoride, but at red heat the reaction proceeds readily. The platinum vessels used for carrying out the reaction are corroded at the higher temperature, giving rise to the formation of a double salt of silver iodide and platinum fluoride.

Moissan (15, 17) reduced the preparation of iodine pentafluoride to a more practical basis. He found that fluorine ignites iodine, burning it with a pale blue flame to yield iodine pentafluoride. Likewise, he showed that fluorine reacts with metallic iodides and hydrogen iodide to produce iodine pentafluoride and the corresponding fluorides. The preparation of iodine pentafluoride was preferably carried out by causing a stream of fluorine to impinge on iodine contained in a platinum boat in a glass tube. The iodine pentafluoride was condensed in a cold end of the glass tube. The physical constants for iodine pentafluoride reported by Moissan and later investigators differ sufficiently from those reported by Gore as to cast doubt on the purity of the material obtained by the English investigator.

Prideaux (20) confirmed the analysis made by Moissan on iodine pentafluoride prepared by direct combination of the elements. In a further study of the reaction, he found that iodine was not soluble in liquid fluorine at atmospheric pressure, nor did any reaction take place between the elements as fluorine distilled from the mixture. When the tube containing iodine and liquid fluorine was sealed off and permitted to become warm, however, a dark color appeared in the fluorine next to the iodine and a reaction occurred with flame. A colorless liquid, iodine pentafluoride, condensed in the tube.

Ruff and Keim (26) devised an improved method for the preparation of iodine pentafluoride. Their apparatus consisted of a large-diameter copper tube connected by a small copper tube to a quartz spiral condenser and a receiver. Fluorine was passed over iodine placed in the large copper tube. The heat of the reaction caused the iodine pentafluoride to distill through the small copper tube and into the quartz condenser. The passage of fluorine was continued until all free iodine in the iodine pentafluoride was removed. The product was purified by redistillation in fused quartz at about 5°C. under reduced pressure, with the condenser kept at −20°C.

Ruff and Braida (25) preferred to have a slight excess of iodine present at the end of the reaction and thus minimize the formation of iodine heptafluoride. They purified iodine pentafluoride by distilling the crude product in quartz apparatus at approximately 10 mm. pressure and taking the fraction over at

−10°C. The residue consisted of iodine pentafluoride and iodine oxyfluoride, the presence of the latter being due to the reaction of some moisture present with the iodine pentafluoride.

B. PHYSICAL PROPERTIES

While Moissan (17), Gore (3, 4), Prideaux (19), and others have reported physical constants for iodine pentafluoride, the most recent and complete data are due to Ruff and Braida (24). These latter investigators have described iodine pentafluoride as a colorless liquid which freezes at 9.6°C. and boils at 98°C. The relation between the vapor pressure (millimeters of mercury) of the solid and temperature (°K.) is given by

$$\log p = 11.764 - \frac{3035}{T}$$

while that of the liquid corresponds to

$$\log p = 8.83 - \frac{2205}{T}$$

At 0°C. the density of the solid is approximately 3.75 g./ml., while at −193°C. it is 4.07 g./ml. The density of the liquid is given by the expression:

$$d = 4.38 - 0.004T$$

C. CHEMICAL PROPERTIES

1. Thermal decomposition (17)

Iodine pentafluoride distills at atmospheric pressure without decomposition. When it is heated to approximately 500°C., however, iodine vapors are produced. An increase in temperature accentuates this change only slightly. It seems highly improbable that fluorine is a dissociation product as well as iodine. Rather, Moissan suggested the possibility of the formation of a higher iodine fluoride, as:

$$7IF_5 \rightarrow I_2 + 5IF_7$$

2. Reactions with metals (17)

Silver, magnesium, copper, mercury, iron, and chromium are only very slightly attacked by iodine pentafluoride even on long contact. Molybdenum and tungsten burn in it after warming. At room temperature the alkali metals when plunged into iodine pentafluoride form a surface coating which stops further action. If the alkali metal is heated to its melting point, however, the reaction becomes so violent as to be almost explosive. Arsenic, antimony, and boron become incandescent or inflame in iodine pentafluoride, yielding iodine and the metalloid fluoride.

3. Reactions with other elements (17)

Iodine pentafluoride is not affected by distillation in hydrogen. At 100°C. it is not attacked by oxygen. The reaction between sulfur and warm liquid iodine pentafluoride results in a mixture containing sulfur hexafluoride and sulfur monoiodide and free iodine in small amounts. Red phosphorus burns vigorously in iodine pentafluoride, yielding iodine and phosphorus trifluoride. Chlorine does not react with iodine pentafluoride when cold, but if the temperature is raised the liquid becomes tinged with yellow. Likewise bromine does not react with iodine pentafluoride when cold, but bromine trifluoride and iodine bromide are formed when the mixture is heated. Iodine is very soluble in iodine pentafluoride, but does not react with it (*vide infra*). In the cold, iodine pentafluoride and carbon react to yield carbon tetrafluoride and iodine.

4. Reactions with inorganic compounds (17)

Iodine pentafluoride reacts violently with water and with aqueous solutions in general. Apparently the hydrolysis proceeds as follows:

$$6H_2O + 2IF_5 \rightarrow 2HIO_3 + 10HF$$

While calcium carbonate and calcium phosphate are inert to iodine pentafluoride, calcium carbide becomes incandescent when warmed with it. When potassium hydride is brought into contact with iodine pentafluoride it glows. The reaction products are hydrogen fluoride, potassium fluoride, and iodine.

Iodine pentafluoride is not soluble in concentrated sulfuric acid, but settles to the bottom of the container when added to it. There a reaction sets in at the interface between the liquids and a regular evolution of bubbles of hydrogen fluoride takes place. Iodine pentafluoride does not dissolve appreciably in concentrated nitric acid and does not react immediately with it.

5. Reactions with organic compounds

In a qualitative manner Moissan (17) noted that iodine pentafluoride reacts with such organic compounds as alcohols, ether, ethyl acetate, carbon tetrachloride, chloroform, *s*-tetrachloroethane, perchloroethylene, trichloroethylene, pyridine, benzene, and hydrocarbon mixtures such as gasoline and turpentine. The reactions with chlorine-containing compounds were characterized by the separation of iodine. Compounds rich in hydrogen yielded hydrogen fluoride and tended to inflame in the iodine pentafluoride.

Ruff and Keim (27) studied the action of iodine pentafluoride on benzene at temperatures below 50°C., the point at which the reaction suddenly became violent. The principal products were hydrogen fluoride, iodobenzene, and carbonized matter. Only a small amount of fluorobenzene was formed.

By maintaining iodine pentafluoride in contact with dry carbon tetrachloride at 30–35°C. for an extended period, Ruff and Keim (27) obtained a gas consisting chiefly of trichlorofluoromethane and a small amount of dichlorodifluoromethane. The reaction mixture contained an orange residue of iodine monochloride, iodine trichloride, and some iodine pentoxide resulting from attack on the glass vessel. Only a few per cent of trichlorofluoromethane was changed to dichlorodifluoromethane when trichlorofluoromethane was passed through boiling iodine pentafluoride and the resulting gas mixture heated first to 125°C. and then to 225°C.

Simons, Bond, and McArthur (35) showed that iodine pentafluoride begins to react with iodoform at the temperature of an ice-salt mixture. In their study the temperature was raised gradually to 80-90°C. as the reaction proceeded, and thereby a product mixture of fluoroform and difluorodiiodomethane in a ratio of about 15 to 1 was obtained. When carbon tetraiodide was a reactant under the same conditions, the product was hexafluoroethane.

Scott and Bunnett (32) found that iodine pentafluoride is partially soluble in dry 1,4-dioxane, and that the addition of an excess of iodine pentafluoride caused the precipitation of colorless crystals of a dioxanate having the formula $IF_5 \cdot C_4H_8O_2$. These crystals hydrolyzed in air and even over sulfuric acid in a desiccator. When hydrolysis was complete, the only solid residue was iodic acid. The melting of the dioxanate was accompanied by decomposition and the evolution of hydrogen fluoride and iodine vapor. The value of the melting point varied from 84°C. to more than 112°C., depending on the manner in which it was determined.

D. PHYSIOLOGICAL ACTION

Hanzlik and Tarr (6) found iodine pentafluoride to be a severe skin irritant, as shown by hyperemia, edema, vesication, necrosis, and ulceration.

III. Iodine Heptafluoride

A. PREPARATION

Moissan (17) observed that at 500°C. iodine pentafluoride began to decompose, liberating iodine vapor. He concluded that this was either a dissociation or a decomposition yielding a new fluoride of iodine. Undoubtedly, Moissan produced iodine heptafluoride by the reaction

$$7IF_5 \rightarrow I_2 + 5IF_7$$

Although he promised to investigate it, he failed to do so.

On redistillation of crude iodine pentafluoride Ruff and Keim (26) observed repeatedly the separation of a compound containing iodine and fluorine which was more volatile than iodine pentafluoride. The amount of this material available, however, was too small to permit its purification and identification. After producing chlorine trifluoride they concluded that iodine heptafluoride should exist and turned to its study.

On passing fluorine into liquid iodine pentafluoride no appreciable amount of a more volatile fluoride was obtained, but when a mixture of iodine pentafluoride and fluorine was heated, iodine heptafluoride was produced. Over the range of 100-270°C. the yield of iodine heptafluoride based on the fluorine used increased with increasing temperature. Platinum apparatus was used. In it at 250-270°C. a conversion of 83 per cent of the fluorine used to iodine heptafluoride was obtained.

The iodine heptafluoride was purified by pumping off silicon tetrafluoride at −90°C., followed by fractional distillation of iodine heptafluoride from the iodine pentafluoride.

B. PHYSICAL PROPERTIES (26)

Pure iodine heptafluoride at room temperature is a colorless gas with a sour, musty odor. It may be cooled to a dense, snow-white powder, to colorless crystals, or to a colorless, mobile, supercooled liquid. The compound sublimes at 4.5°C. and melts at 5–6°C.

The molecular weight based on determinations of vapor density at room temperature was found to average 260.2, while theory calls for 260.3. Ruff and Keim claimed that this indicated no association at a little above the boiling point.

The vapor pressure of the solid determined on a freshly sublimed sample was found to correspond to the expression:

$$\log p = 8.6604 - \frac{1602.6}{T}$$

C. CHEMICAL PROPERTIES (26)

1. Reactions with metals

With the possible exception of elements in the platinum group, iodine heptafluoride appears to react with all metals. The extent of the reaction seems to be determined by the stability of the fluoride film formed on the metal.

Copper and silver tarnish slightly when heated with iodine heptafluoride. Likewise, a stable film is formed on the surface of mercury which, even on moderate heating, protects the remainder of the metal from the iodine heptafluoride.

Iron, chromium, and cobalt react at a red heat, yielding compounds of undetermined composition. Molybdenum and tungsten form the volatile compounds molybdenum hexafluoride and tungsten hexafluoride. Thus these metals on slight warming with iodine heptafluoride react readily and completely.

The reactions of iodine heptafluoride with sodium, potassium, barium, magnesium, aluminum, and tin are vigorous and are accompanied by the evolution of heat and light. Reaction takes place immediately with the first three metals, but heating is required for the last three, since they are protected by a fluoride film at room temperature.

2. Reactions with other elements (26)

Sulfur reacts with iodine heptafluoride at room temperature producing iodine and sulfur fluorides of undetermined composition, but selenium and tellurium require heating to undergo the same type of reaction. Arsenic, phosphorus, boron, and silicon all react at room temperature to give the corresponding fluorides, iodine pentafluoride, and iodine.

Iodine reacts with iodine heptafluoride to produce iodine pentafluoride. Chlorine reacts with iodine heptafluoride with the formation of iodine monochloride, iodine trichloride, and chlorine monofluoride. Bromine, however, was found not to react with iodine heptafluoride. (This observation should be checked, for the formation of iodine bromide and bromine trifluoride would be expected to occur.)

While iodine heptafluoride was inert to hydrogen at room temperature, heating a mixture of the materials gave rise to reactions of explosive violence. A mixture of 1 volume of iodine heptafluoride and 3.5 volumes of hydrogen was exploded by an electric spark into hydrogen fluoride, hydrogen iodide, and some iodine.

Pure activated carbon immediately caught fire in iodine heptafluoride and free iodine was liberated.

3. Reactions with inorganic compounds (26)

Water quietly dissolved gaseous iodine heptafluoride, forming periodate and fluoride ions.

After being warmed slightly, carbon monoxide burned in iodine heptafluoride with a pale yellow flame. In the form of compact quartz silica was attacked only slowly by iodine heptafluoride, but in the form of glass it reacted with it more readily. With nitric oxide at room temperature iodine heptafluoride formed nitroxyl fluoride, nitrosyl fluoride, and iodine pentafluoride. Tungstic oxide and molybdic oxide reacted after heating with iodine heptafluoride to form oxyfluorides, but phosphorus pentoxide even on heating showed only a slight reaction.

Potassium bromide, silver nitrate, and sodium carbonate all reacted with iodine heptafluoride, but the reaction products were not determined satisfactorily. In the first case, it was observed that bromine was liberated. Silver iodide and metallic silver were the only products reported in the silver nitrate reaction. Sodium carbonate was merely observed to become hot in contact with iodine heptafluoride.

4. Reactions with organic compounds (26)

Organic compounds in general have been found to react with iodine heptafluoride to produce complex mixtures of degraded organic fluorides and iodine.

Benzene and light paraffin hydrocarbons took fire at once in iodine heptafluoride. This was also true of alcohol and ether. Methane burned to form hydrogen fluoride, iodine, and (presumably) carbon tetrafluoride, with no free carbon separating.

Paraffin oils, stopcock grease, cotton, and cellulose reacted slowly or with flame, depending on the amount of iodine heptafluoride present. Such oxygen-containing materials as acetone, acetic acid, and ethyl acetate reacted immediately and were heated by the reaction to boiling. The products in these cases included hydrogen fluoride, iodine pentoxide, and highly volatile organic fluorides.

Pyridine united with iodine heptafluoride with the evolution of considerable heat to form an orange product of undetermined composition.

Chloroform, carbon tetrachloride, tetrachloroethane, perchloroethylene, and trichloroethylene all reacted to yield a mixture of gases having a sweet odor.

IV. LOWER FLUORIDES OF IODINE (25)

The available information indicates that no fluoride of iodine lower than iodine pentafluoride has a stable existence. Measurements of the vapor pressure and melting point of a mixture of iodine pentafluoride and iodine gave no evidence of a lower fluoride. Fractional distillation of the mixture yielded only iodine and iodine pentafluoride. The direct reaction of iodine and fluorine to iodine pentafluoride or iodine heptafluoride further points to the absence of a compound like iodine trifluoride.

V. Bromine Monofluoride

A. PREPARATION

The existence of the monofluoride of bromine was suspected by Ruff and Menzel (30) when they noted that the product of the reaction of bromine trifluoride and bromine had a higher vapor pressure and a stronger etching action on vitreous quartz than bromine trifluoride, bromine pentafluoride, or bromine.

Ruff and Braida (24) undertook the preparation of bromine monofluoride, but were unable to obtain it in a pure form because of its instability. Mixtures of bromine trifluoride, bromine pentafluoride, bromine, and bromine monofluoride were produced by the reaction of fluorine and bromine diluted by nitrogen at 10°C. The reaction product was fractionally condensed at the successively lower temperatures of 10°, −20°, −50°, −120°, and −185°C. Based on analysis, density, and vapor-pressure data, the conclusion was reached by Ruff and Braida that the mixture condensed in one of the −120°C. traps contained almost 50 per cent bromine monofluoride. The present reviewers do not find the evidence altogether convincing.

B. PHYSICAL PROPERTIES

Ruff and Braida (24) estimated the boiling and freezing points of bromine monofluoride to be −20°C. and −33°C., respectively. The gas, liquid, and solid phases of bromine monofluoride were reported as being red-brown, red, and the color of dichromate, respectively.

C. CHEMICAL PROPERTIES

The chemical properties of bromine monofluoride are reported to resemble those of the other bromine fluorides in general. Its outstanding property is its thermal instability. At 50°C. the decomposition into bromine and bromine trifluoride was found to be so rapid that bromine monofluoride could no longer be detected. This low stability was found to be further decreased by exposure to light.

Bromine monofluoride quickly destroyed vitreous quartz and attacked gold and platinum vigorously under conditions which left these materials unaffected by bromine and fluorine.

VI. Bromine Trifluoride

A. PREPARATION

Moissan (16) found that fluorine combined violently with bromine vapor in the cold with "une flamme éclairante." When fluorine was passed through liquid bromine, combination was also immediate but without flame. The composition of the product was first established by Lebeau (8, 9, 10, 11) and was almost immediately verified by Prideaux (20) as corresponding to bromine trifluoride.

Lebeau prepared bromine trifluoride in a platinum crucible by passing fluorine beneath the surface of dry liquid bromine. The crucible itself was contained in a large glass cylinder judiciously cooled by dry ice to maintain a temperature slightly above the freezing point of bromine (−7.2°C.). The reaction was immediate and quite regular. The bromine trifluoride condensed completely in the crucible and formed an upper liquid layer rather insoluble in the liquid bromine. The bromine trifluoride dissolved enough bromine to give the resulting solution a yellow color.

Bromine trifluoride was also formed when metallic bromides were decomposed by fluorine (9):

$$KBr + 2F_2 \rightarrow KF + BrF_3$$

Ruff and Menzel (30) prepared bromine trifluoride by reacting fluorine with bromine at 200°C. (*vide infra*).

B. PHYSICAL PROPERTIES

Ruff and Braida (23, 24) found bromine trifluoride to be a colorless liquid which solidified at 8.8°C. At the melting point the density of the solid was 3.23 g./ml. and that of the liquid was 2.843 g./ml. The variation of the liquid density with absolute temperature is given by the equation:

$$d = 3.623 - 0.00277T$$

Ruff and Braida (24) determined the vapor pressure of bromine trifluoride between 3.8 and 136 mm. of mercury in platinum apparatus of the Smith–Menzies type. The vapor pressure–absolute temperature relation could be expressed by the equation:

$$\log p = 8.41954 - \frac{2220.2}{T}$$

From this equation the boiling point was calculated to be 127.6°C. This extrapolated value appears to be too low, since Lebeau (8) by direct measurement was able to report a boiling point between 130° and 140°C.

By the use of the Clausius–Clapeyron equation and their vapor-pressure data Ruff and Braida showed that the heat of vaporization of bromine trifluoride was about 10 kg.-cal. per mole. Trouton's constant was calculated to be 25.3.

C. CHEMICAL PROPERTIES

1. Reactions with elements (8, 9, 10, 11)

Boron, silicon, powdered arsenic, and powdered antimony all burned in liquid bromine trifluoride with the evolution of heat and light. A crystal of iodine when placed on solid bromine trifluoride at first merely stained it brown. Then the bromine trifluoride melted rapidly and reacted with incandescence, evolving iodine pentafluoride and bromine vapor. The reaction was strongly exothermic. Sulfur, like iodine, did not appear to react with solid bromine trifluoride, but it inflamed vigorously with liquid bromine trifluoride, giving a mixture of the fluorides and bromides of sulfur. Graphite was not changed in the cold. Lampblack absorbed the liquid and when warmed slightly burned with a flash.

2. Reaction with water

Bromine trifluoride was found by Lebeau (8) and Prideaux (20) to react vigorously with water to give oxygen and an aqueous solution of hydrofluoric acid, hypobromous acid, and bromic acid. The reaction with aqueous alkali produced oxygen and the salts of the metals.

3. Reactions with organic compounds

Lebeau (8) and Ruff and Braida (23) observed that bromine trifluoride reacted violently with organic compounds. Ether, benzene, and turpentine took fire on contact with it. Methyl chloride at first dissolved bromine trifluoride, and then reacted with explosive violence. In none of these cases was the reaction controlled to give desired products.

Nutting and Petrie (19) have described the preparation of chlorofluoromethanes by the controlled action of bromine trifluoride on carbon tetrachloride.

McBee, Lindgren, and Ligett (13) carried out the preparation of a mixture corresponding approximately to the formula $C_6Br_2Cl_4F_6$ by the action of bromine trifluoride on perchlorobenzene and a mixture approximating $C_6Br_2Cl_3F_6(CF_3)$ when pentachloro(trifluoromethyl)benzene was the organic reactant. These mixtures were intermediates in the preparation of perfluorobenzene and perfluorotoluene, respectively.

D. PHYSIOLOGICAL ACTION

Hanzlik and Tarr (6) found bromine trifluoride to be a severe skin irritant, as shown by hyperemia, edema, vesication, necrosis, and ulceration.

VII. BROMINE PENTAFLUORIDE

A. PREPARATION

The successful preparation of iodine heptafluoride by the high-temperature combination of iodine pentafluoride and fluorine suggested that bromine pentafluoride might be made in a similar manner. Ruff and Menzel (30) heated bromine trifluoride to 90–100°C., mixed the bromine trifluoride vapors with fluorine, and then heated the mixture to 200°C. in a platinum tube. By fractional condensation of the gaseous products bromine pentafluoride was separated from the reaction mixture.

After an explosion, however, the two-step process in platinum was abandoned by Ruff and Menzel in favor of direct combination of bromine and fluorine to bromine pentafluoride in a copper apparatus at 200°C. Purification was accomplished by condensing the entire reaction mixture and then fractionally distilling it in quartz.

B. PHYSICAL PROPERTIES (30)

Ruff and Menzel showed bromine pentafluoride to be a colorless liquid which solidified at −61.3°C. and boiled at 40.5°C. The molecular weight at 330 mm. and 29°C. was found to be 174.7, while theory calls for 174.92. The claim was made that this excellent agreement shows no association of the molecules in the gas phase.

The relation between the vapor pressure of liquid bromine pentafluoride and absolute temperature was shown to be represented by the equation:

$$\log p = 8.0716 - \frac{1627.7}{T}$$

The heat of vaporization at the boiling point was calculated to be 7443 cal. per mole. Trouton's constant was calculated to be 23.7.

The density of solid bromine pentafluoride at the melting point was found to be 3.09 g./ml., while the following equation was shown to give the relation between the liquid density and absolute temperature:

$$d = 3.496 - 0.00346T$$

C. CHEMICAL PROPERTIES (30)

It appears probable that bromine pentafluoride reacts with every known element except the rare gases and nitrogen and oxygen. With the exception of the inorganic fluorides, there is little doubt that it reacts under proper conditions with the vast majority of inorganic compounds. Even under mild reaction conditions, it attacked organic compounds vigorously.

1. Reactions with metals

There is no recorded failure of bromine pentafluoride to react with a metal. These reactions usually proceed sufficiently rapidly to be accompanied by a sharp rise in temperature and the emission of light. Little is known about the reaction products, except that they contain metallic fluorides. The main difference observed in these reactions is the ease with which they are initiated. The major portion of this difference is probably due to the varying effectiveness of the fluoride films first formed as a means of protection for the main body of metal.

Ruff and Menzel found that lithium powder, barium, zinc, mercury, molybdenum, tungsten, iron, cobalt, arsenic, and antimony react immediately with bromine pentafluoride at room temperature. Bismuth, gold, and manganese in bulk form and powders of aluminum, nickel, rhodium, and iridium required slight warming. Still higher temperatures ranging from about 300°C. to a dull red heat were necessary for the reaction of bromine pentafluoride with sodium, magnesium, calcium, cadmium, copper, tin, chromium, powdered titanium, and platinum.

2. Reactions with other elements

Ruff and Menzel found that powdered boron, carbon, and sulfur reacted immediately and vigorously with bromine pentafluoride, as did red phosphorus, selenium, and tellurium in bulk form. The exact nature of the products was not determined. Although iodine reacted with bromine pentafluoride at room temperature, heating to 250–300°C. was necessary to initiate reactions with chlorine and fluorine. The compositions of the halogen fluoride mixtures which resulted were not reported. Bromine pentafluoride reacted with bromine at 250°C. to give bromine trifluoride.

A violent explosion resulted when a mixture of bromine pentafluoride and hydrogen was ignited by a flame.

3. Reactions with inorganic compounds

Ruff and Menzel (30) reported that bromine pentafluoride reacted immediately with the following oxides, liberating heat: tungstic oxide, molybdic oxide, chromic acid, phosphorus pentoxide, iodine pentoxide, arsenic pentoxide, boric oxide, cadmium oxide, and magnesium oxide. Moderate warming was necessary to start the reaction with silica (kieselguhr) and with glass. While sulfur dioxide and carbon monoxide also reacted, ignition in a flame was required. Bromine pentafluoride reacted violently with water. Ruff and Menzel (30) suspected that the products were bromine oxyfluoride ($BrOF_3$) and hydrogen fluoride, but did not establish the point.

Sodium chloride and potassium bromide both reacted immediately with bromine pentafluoride to evolve chlorine and bromine, respectively. Potassium iodide and ammonium chloride inflamed instantly with bromine pentafluoride. Sodium nitrite, potassium nitrate, and nitric acid reacted with evolution of gases. Ammonia inflamed in bromine pentafluoride, and both sodium hydroxide and sulfuric acid reacted with it evolving heat.

4. Reactions with organic compounds

Ruff and Menzel (30) reported that reactions between bromine pentafluoride and organic compounds are usually accompanied by flame and often approach explosive violence. There is no recorded instance of a desired organic fluoride being made by the use of bromine pentafluoride. These generalizations are borne out by the action of bromine pentafluoride on such widely different organic materials as methane, acetic acid, ethanol, benzene, cork, picein, cotton, paper, textiles, and rubber.

VIII. CHLORINE MONOFLUORIDE

A. PREPARATION

The history of the preparation of chlorine monofluoride is remarkable for the number of failures to prepare it. Moissan (15, 16) found no apparent reaction when fluorine and chlorine were mixed at room temperature. Lebeau (8, 11) remarked that one may conclude that fluorine and chlorine do not react either directly or indirectly at room temperature, since fluorine displaces chlorine from chlorides without producing a chlorine fluoride. Lebeau also observed that fluorine dissolved freely in liquid chlorine at −80°C., but there was no indication that any definite compound was formed. The solution evolved fluorine when cooled to the freezing point of chlorine.

Ruff and Zedner (31) struck an electric arc in a solution of fluorine in liquid chlorine without success.

The first bit of progress was accomplished by Ruff and Ascher (22) in their investigation of the action of hydrogen chloride gas on liquid fluorine. When the hydrogen chloride came in contact with the fluorine gas above the liquid fluorine surface, a greenish light was observed and a white floc settled slowly in the liquid fluorine. Fractionation yielded an orange-colored liquid boiling between −100° and −80°C., but the quantity of this product was too small to permit identification.

Ruff and Ascher (22) had observed, however, that explosions occurred in their preparation of rhodium trifluoride by the passage of fluorine over the trichloride. They then passed a 2:1 mixture of fluorine and chlorine at 400°C. through a quartz tube containing a fluorite boat filled with rhodium to act as a catalyst. The condensate from this process contained an orange-red liquid which etched the quartz, with the formation of silicon tetrafluoride.

Because of this reactivity toward quartz, their later studies of the reaction between fluorine and chlorine were carried out in a copper block heated by an oil bath to 250°C. It was observed that the presence of rhodium was not necessary and that the union of fluorine and chlorine was accompanied by the evolution of heat and by occasional explosions. The chlorine monofluoride was isolated by the fractional condensation of the reaction products.

Ruff *et al.* (21) concluded that the reaction proceeds to an equilibrium and that even in the presence of a great excess of fluorine the product still contains free chlorine. They regarded the formation of chlorine monofluoride as due to the action of nascent chlorine on fluorine and indicated that it should be possible to find catalysts which would permit the reaction to proceed at lower temperatures with better yields.

Fredenhagen and Krefft (2), however, disposed of these views by sparking a mixture of chlorine and fluorine at room temperature and observing that a yellow-red flame spread through the mixture. The reaction resulted in either a detonation or a gentle "puff", depending on the mixture. In the absence of moisture there was no explosion. Fredenhagen and Krefft concluded that fluorine and chlorine actually have a great affinity for each other, and that Ruff's method of preparation prevented the combination of the elements from going to completion.

Ruff and Krug (28) found that a mixture of four parts of chlorine monofluoride and one part of chlorine trifluoride resulted from the reaction of fluorine with chlorine at −170°C. in the volume ratio of three to two.

B. PHYSICAL PROPERTIES

Ruff and Laass (29) found chlorine monofluoride at room temperature to be a colorless gas with a characteristic odor different from both that of fluorine and that of chlorine. In fused quartz it exhibits an orange cast, which is perhaps due to the presence of traces of chlorine monoxide formed from reaction with quartz. At −100.8°C. chlorine monofluoride condenses to a yellowish liquid and at −154°C. it freezes to a white solid.

The vapor pressure of the liquid corresponded to the expression:

$$\log p = 15.738 - \frac{3109}{T} + \frac{1.538(10)^5}{T^2}.$$

where p is millimeters of mercury and T is °K.

Ruff and Laass found the heat of formation of chlorine monofluoride to be 25.7 kg.-cal. per mole. This value was based on their determination that

$$\text{ClF} + \text{H}_2 \rightarrow \text{HCl} + \text{HF} + 58.6\text{ kg.-cal.}$$

and Ruff's value of 62.3 kg.-cal. per mole for the heat of formation of hydrogen fluoride.

Wahrhaftig (36), from a study of the absorption spectrum of chlorine monofluoride between 3500 Å. and 7000 Å., and particularly a band at 4800 Å., concluded that while the heat of formation of chlorine monofluoride is appreciable, the value of 25.7 kg.-cal. per mole is too high.

C. CHEMICAL PROPERTIES (22)

1. Reactions with metals

Like fluorine and the other halogen fluorides, chlorine monofluoride appears to react with all metals, with the differences in degree being due to the varying protective qualities of the films of metallic fluoride originally formed. With chlorine monofluoride, sodium forms a white protective layer in the cold but inflames on heating. Magnesium and aluminum burn in chlorine monofluoride when heated strongly. Copper and zinc as powders and gold and platinum as foils react on slight heating. Iron powder glows on contact with chlorine monofluoride at room temperature. Mercury at first forms a brown-black coating, but on heating yields a white sublimate.

Arsenic, antimony, and amorphous boron all burn briskly at room temperature to arsenic pentafluoride, antimony pentafluoride and, presumably, boron trifluoride.

2. Reactions with other elements

Hydrogen required some heating before it ignited and burned in chlorine monofluoride. Bromine and iodine reacted to produce bromine trifluoride and, probably, iodine pentafluoride. Sulfur reacted slowly and without flame, but phosphorus burned briskly in chlorine monofluoride at room temperature.

3. Reactions with inorganic compounds

Chlorine monofluoride reacted vigorously with water. Oxygen and ozone were among the products formed. After warming, carbon monoxide and sulfur dioxide both reacted with chlorine monofluoride.

4. Reactions with organic compounds

No controlled reaction with any organic compound was observed. Under the test conditions paraffin oil, filter paper, cork, picein, and other organic materials all caught fire in chlorine monofluoride.

IX. CHLORINE TRIFLUORIDE

A. PREPARATION

The first evidence pointing toward the existence of chlorine trifluoride was obtained by Ruff and Laass (29) during their determination of the latent heat of evaporation of chlorine monofluoride. While carrying out their experiments on samples of chlorine monofluoride successively boiled off from the same storage vessel, these investigators obtained an increase in their values of the heat of evaporation. The presence of a higher fluoride in the chlorine monofluoride would account for the trend observed in these measurements.

Accordingly, Ruff and Krug (28) undertook the preparation of chlorine trifluoride. Since it was suspected that a low temperature would favor a good yield, 3 volumes of fluorine and 2 volumes of chlorine were passed into a quartz ampoule held at −170°C. Combination of the elements took place, yielding one part of crude chlorine trifluoride to four parts of chlorine monofluoride. By using 800 ml. of chlorine and 1200 ml. of fluorine per hour for 8 hr., there were prepared about 5 ml. of liquid chlorine trifluoride and 20 ml. of chlorine monofluoride. The chlorine was completely consumed.

The proportion of chlorine trifluoride in the reaction product appeared to be much greater at low temperatures than at high. While the ratio of chlorine monofluoride to chlorine trifluoride is approximately four to one at −170°C., at 250°C. the number of moles of chlorine monofluoride is many times that of chlorine trifluoride.

The production of chlorine trifluoride in Germany in pilot-plant quantities during the recent war has been reported (1, 18). The compound was made by heating the proper proportion of the gaseous elements to 280°C. in a U-shaped tube. The vapors were condensed at −80°C. and run into iron cylinders which were vented several times to allow fluorine, chlorine, and chlorine monofluoride to escape.

Apparently, the German Army intended to use chlorine trifluoride in shells against aircraft and tanks because of its incendiary properties (*vide infra*).

B. ANALYSIS

For analysis, chlorine trifluoride was distilled by Ruff and Krug (28) into a quartz tube which was cooled in liquid air, sealed off in a flame, and then weighed. The tube was broken under 10 per cent sodium hydroxide, which immediately reacted with the chlorine trifluoride. The hypochlorites were reduced by digesting with hydrazine hydrate or pieces of zinc. The total solution was made up to a known volume, from which aliquot portions were taken for the determination of fluoride as calcium fluoride and chloride as silver chloride. It was necessary to complete the reduction of hypochlorites by digesting several times with sulfurous acid after the silver nitrate solution had been added. In two trials the atomic ratio of chlorine to fluorine was found to be 1:2.997 and 1:3.07.

C. PHYSICAL PROPERTIES (28)

While in the liquid phase chlorine trifluoride has a pale green color, as a gas it is practically colorless. In the solid state it is white.

Chlorine trifluoride melts at −83°C. In the liquid phase the vapor pressure is given by the equation

$$\log p = 7.42 - \left(\frac{1.292(10)^3}{T}\right)$$

from which it can be seen that the boiling point is 11.3°C. At the boiling point the latent heat of evaporation is close to 5.9 kg.-cal. per mole, and the Trouton constant is 20.8. The critical temperature is estimated by the "three halves rule" to be 154°C.

In three trials by the density method, the molecular weight of the chlorine trifluoride gas was measured at 86.71, 87.49, and 87.93; theory requires 92.46 Whether the discrepancy is due to partial dissociation or to impurities is uncertain.

D. CHEMICAL PROPERTIES (28)

It appears probable that chlorine trifluoride reacts with every element except the rare gases, nitrogen, and possibly platinum and palladium. There is little doubt that it reacts under proper conditions with the vast majority of inorganic and organic compounds.

1. Reactions with metals

While some metals such as magnesium, aluminum, and copper form a protective fluoride film which can halt further action, at elevated temperatures these metals combine explosively with chlorine trifluoride. To varying extents this is true of other metals, including silver, lead, zinc, tin, sodium, and calcium. Although potassium, molybdenum, tungsten, iron, rubidium, iridium, and osmium are reported to inflame in chlorine trifluoride, it seems likely that under proper conditions protective fluoride films can be built up on at least some of these metals.

2. Reactions with non-metals

Such representative non-metals as silicon, red phosphorus, arsenic, antimony, sulfur, selenium, tellurium, bromine, and iodine inflame on contact with chlorine trifluoride.

3. Reactions with organic compounds

Organic compounds, even graphite and wood charcoal, react vigorously with chlorine trifluoride. Some of these reactions approach explosive violence. The behavior of benzene, ether, carbon tetrachloride, acetic acid, paraffin wax, cotton, and wool when brought in contact with chlorine trifluoride supports the generalization.

4. Reactions with hydrogen and other gases

Hydrogen, sulfur dioxide, hydrogen sulfide, ammonia, and illuminating gas all ignite in chlorine trifluoride.

5. Reactions with inorganic compounds

Chlorine trifluoride reacts actively with the following oxides: H_2O, MgO, CaO, Al_2O_3, La_2O_3, TiO_2, SnO_2, PbO_2, U_2O_5, Ta_2O_5, CrO_3, Cr_2O_3, MoO_3, WO_3, MnO_2, P_2O_5, B_2O_3, and As_2O_3. While no reaction is reported with ZnO, HgO, SiO_2, ZrO_2, ThO_2, and Fe_2O_3, it is probable that this is just a matter of test conditions. At an elevated temperature or in the presence of a trace of water these oxides should also react.

In the presence of chlorine trifluoride lively reactions are undergone by the following: potassium iodide, mercuric iodide, potassium carbonate, silver nitrate, sulfuric acid, nitric acid, and tungsten carbide. Under the conditions employed, no reaction was observed with sodium chloride, potassium sulfate, potassium nitrate, mercuric sulfate, and mercuric chloride.

X. HIGHER FLUORIDES OF CHLORINE

As yet no evidence has appeared to indicate the existence of higher fluorides of chlorine than chlorine trifluoride. The one mention of chlorine pentafluoride (33) was a typographical error (34).

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THE ELECTRICAL DOUBLE LAYER AND THE THEORY OF ELECTROCAPILLARITY[1]

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The theory of the electrical double layer is discussed with particular reference to those aspects of the subject usually included under the heading "electrocapillarity". Modern values for the thermodynamic properties of the double layer are presented for typical substances, and references are given to that part of the literature which is likely to be of interest in connection with the problems here discussed.

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I. INTRODUCTION

The review[3] which follows deals with the theory of electrocapillarity and its relation to the problems of elucidating the structure of the electrical double layer. The theory of electrokinetic phenomena is not discussed.

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[2] Publication of this paper was delayed by the loss of the original manuscript in transit.

[3] The symbols used in this paper are listed below. All capacities and charges are per square centimeter of interface.

C = differential capacity of the electrical double layer
C^d = differential capacity of the diffuse double layer
C^o = differential capacity of the region between a metallic surface and the outer Helmholtz plane
C_i = differential capacity of the region between a metallic surface and the inner Helmholtz plane
D = dielectric constant
D_0 = diabattivity of free space (= $4\pi \times$ permittivity of free space)
E = electrical potential difference at an ideal polarized electrode as read on the potential-fixing potentiometer
$\mathbf{E}$ = electrical potential difference at an ideal polarized electrode relative to the potential of the electrocapillary maximum
$\mathcal{E}$ = electrical potential difference at an ideal polarized electrode as read on the potential-fixing potentiometer when the reference electrode is a normal calo-

The terms "electrocapillarity" and "electrical double layer" are not commonly well understood. A satisfactory definition of the first must await a discussion of the ideal polarized electrode, another unfamiliar term, but we may state meanwhile that electrocapillarity is the study of the surface tension of metals in contact with inert salt solutions, together with the study of all of the effects with which this is connected. The term "electrocapillarity" arises from the fact that most of the early studies in the field were done with the Lippmann capillary electrometer.

The electrical double layer is the array of charged particles and oriented dipoles which is thought to exist at every interface. Very often the term is used in a narrower sense to mean the array of charges and dipoles between two immiscible media when one is a salt solution. It is in this narrower sense that the term is here used.

The concept of the electrical double layer is due to Quincke (80), although that term was not used by him. The double layer was thought to consist of two layers of charge, one positive and one negative, situated at the interface. Today the

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mel electrode and when liquid-junction potentials have been eliminated as well as possible

$E^-(E^+)$ = electrical potential difference E when the reference electrode is simply reversible to the anion (cation) of a salt solution

F = Faraday's constant

K = integral capacity of the electrical double layer

K^d = integral capacity of the diffuse double layer

K^o = integral capacity of the region to which C^o refers

K^i = integral capacity of the region to which C^i refers

k = Boltzmann's constant

M = molar concentration of a solution

m = molal concentration of a solution

n_{0i} = number of ions of type X_i in unit volume of solution measured at a point remote from the double layer

n_i = number of ions of type X_i in unit volume of solution measured at a point within the double layer

q = electronic charge of the electrical double layer

r = radius of an adsorbed anion or distance from the interface to the inner Helmholtz plane

T = absolute temperature

w_i = work required to move an ion of type X_i from the interior of a designated position within the double layer

X_i = an ion or neutral molecule of type designated by the subscript i

x = distances measured from the physical interface

z = absolute value of the valence of an ion

$z_-(z_+)$ = valence of an anion (cation) including sign

z^i = maximum number of ions of type X_i which can be adsorbed at 1 sq. cm. of an interface

z_{0i} = maximum number of ions of type X_i for which there is space in 1 cc. of solution

α = the metallic phase of an ideal polarized electrode

β = the non-metallic phase of an ideal polarized electrode

Γ_i = superficial density of a component of type X_i as involved in the Gibbs adsorption equation point of view is somewhat more complicated, although the name persists even in those cases where it is plainly inappropriate.

Briefly the electrical double layer may consist of a layer of electrons (if the non-electrolytic phase is a metal or electronic conductor), a layer of adsorbed ions, and a *diffuse* double layer consisting of an ionic atmosphere in which ions of one sign are in excess of their normal concentrations whereas those of the other sign are in defect. This atmosphere of abnormal concentrations of ions falls off rapidly as one recedes from the surface, the half-thickness of the charge density being seldom over 100 Ångströms and usually much less. Finally, there may exist at the interface a thin (often monomolecular) layer of neutral molecules which, whether they are oriented or not, exert an influence on the thermodynamic properties of the interface. Diagrams of the electrical double layer are given later (figures 17-19), after the theory upon which they are based has been presented.

Metal-solution interfaces lend themselves to the exact study of the double layer better than other types because of the possibility of varying the potential differ-

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$\Gamma_+(\Gamma_-)$ = superficial density of cations (anions)
Γ_s = superficial density of entropy at an interface
γ = mean activity coefficient of the ions of a strong electrolyte
ϵ = charge on a single univalent cation
η = total charge of the solution phase of the electrical double layer ($= -q$)
η^d = charge of the diffuse double layer
$\eta^d_-(\eta^d_+)$ = contribution of any excess or deficiency of anions (cations) to the charge of the diffuse double layer
η^i = charge of the compact (adsorbed) part of the double layer
$\eta^i_-(\eta^i_+)$ = charge of the compact part of the double layer when the adsorbed ions are anions (cations)
κ = a measure of the reciprocal thickness of the diffuse double layer defined by equation 57
μ = chemical potential of a neutral molecular species
$\mu_-(\mu_+)$ = chemical potential of an anion (cation)
μ_i = chemical potential of a component X_i
$\nu_+(\nu_-)$ = number of cations (anions) furnished by the dissociation of one molecule of a salt
$\nu = \nu_+ + \nu_-$
ρ = charge density (charge per unit volume)
σ = interfacial tension
ϕ^i_- = specific adsorption potential of an anion
ψ = electrical potential at any point within the double layer relative to the interior of the solution phase
ψ^r = rational potential difference between dissimilar phases
ψ^o = electrical potential of outer Helmholtz plane relative to the interior of the solution phase
ψ^i = electrical potential of inner Helmholtz plane relative to the interior of the solution phase
$\psi^\alpha(\psi^\beta)$ = cavity potential (i.e., electrostatic potential) of the metallic (non-metallic) phase
ψ^{I} = cavity potential of a copper wire attached to the metallic phase
ψ^{II} = cavity potential of a copper wire attached to the reference electrode
MAX = subscript or superscript referring to the electrocapillary maximum

ence between the phases without varying the composition of the solution. This is done through the use of a reference electrode and a potentiometer which fixes the potential difference in question. In favorable cases there is a range of potentials for which a current does not flow across the interface in a system of this kind, the interface being electrically similar to a condenser of large specific capacity. The capacity of this condenser gives a fairly direct measure of the electronic charge on the metallic surface, and this, in turn, leads to other information about the double layer. No such convenient and informative procedure is possible with other types of interfaces, a fact which explains the preoccupation with such systems in the present review.

Of the metals which might be used for the purpose outlined, mercury is preëminent. Being a liquid, its surface is readily cleaned, it is free from mechanical strains, and its interfacial tension is readily measured. In addition, mercury is distinguished by its low chemical activity and high hydrogen overvoltage. The latter characteristic makes it possible to work at potentials which would otherwise be objectionable because of a rapid evolution of hydrogen from the reduction of the solvent. Nearly everything one desires to know about the electrical double layer is ascertainable with mercury surfaces if it is ascertainable at all.

II. THE IDEAL POLARIZED ELECTRODE

For an understanding of electrocapillary phenomena, an understanding of the ideal polarized electrode is prerequisite. This type of electrode is observed only with high-overvoltage metals, and then only in approximation. It is a type very different from the reversible electrodes with which one deals in thermodynamic discussions of galvanic cells, yet it is reversible and at equilibrium.[4] Its importance rests upon the fact that it can be treated by exact thermodynamic means.

The rigorous definition of an ideal polarized electrode is as follows (46): It is a system composed of a metal in contact with an electrolytic solution for which, at equilibrium, the concentration of every charged component is finite in one phase *only*. As applied to electrons, this statement is to be taken to mean that there exists in the solution phase no finite amount of any component which can take up or give up finite amounts of electricity from the metallic phase.

This definition calls for some amplification. In the first place it is necessary to state what are regarded as charged components. The metallic phase is thought of as composed of two charged components, electrons and metallic ions. The solution phase is thought of as composed of neutral solvent molecules and of ions of whatever sort may be present. These ions are the charged components of the phase. If dissolved hydrogen is present and if its equilibrium with hydronium ions is to be considered, this is regarded as consisting of protons and electrons, both of which are charged components. Hydrogen ions are regarded as hydrated protons. Dissolved oxygen is thought of as oxide ions plus electrons. Hydroxyl ions are similarly thought of as hydrated oxide ions. In general, if two substances are present which can be converted into one another by the addition or removal of charge, these two forms are regarded as forms of the same basic component, the more reduced form of which is composed of electrons plus the other. The reason for this procedure concerning the choice of components is that it makes it easier to develop the thermodynamic theory of electrocapillarity in a rigorous manner.

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[4] The latter point is not always conceded. It is discussed in what follows.

The definition of an ideal polarized electrode is chosen so that passage of charge across the interface shall not take place spontaneously at equilibrium. More exactly stated, when the potential difference between the phases is altered slightly, no finite amount of charge must cross the interface of an ideal polarized electrode during the reëstablishment of equilibrium. This is a corollary of the definition, because if charge did cross the interface, finite amounts of some charged component would then be present in both phases, contradicting the requirement of the definition. Experimentally, the ideal polarized electrode is an electrode which behaves like an electrical condenser without leakage. Its capacity arises from the fact that charges may approach or recede from the interface, though they do not cross it.

This definition of an ideal polarized electrode is too strict ever to be fully realized in the laboratory, but close approximations to it are possible, and, what is more important, the deviations which are unavoidable are of negligible effect, as will presently be shown.

An example will serve to illustrate the definition and also to bring out additional points of importance. Consider a clean mercury electrode in an aqueous 1 *M* potassium chloride solution (completely deaërated) into which is immersed a normal calomel electrode. Between the mercury in the calomel electrode and the clean mercury electrode there is inserted a potentiometer and, optionally, a galvanometer. The clean mercury electrode is attached to the negative end of the potentiometer. No continuous current flows through the circuit if the potential is not made too large. This system may have any number of conditions of equilibrium, depending upon the setting of the potentiometer. For definiteness, consider that $-E$, the potentiometer reading, is 0.556 volt, in which case q, the electronic charge on the mercury surface, will be zero,[5] as we shall show later. Under these circumstances the following reactions are all conceivable, any one of which would result in transferring charged particles from one phase to the other in violation of our definition of an ideal polarized electrode.

Reaction	*Equilibrium concentration*
$2Hg \rightarrow Hg_2^{++} + 2e^-$	$c_{Hg_2^{++}} = 10^{-36}$ moles per liter
$K^+(aq) + e^- \rightarrow K$ (in Hg)	$N_K = 10^{-45}$ moles per mole
$2Cl^- \rightarrow Cl_2 + 2e^-$	$p_{Cl_2} = 10^{-28}$ atm.
$2H_2O + 2e^- \rightarrow H_2 + 2OH^-$	$p_{H_2} = 4 \times 10^{-8}$ atm.

If the electrode is ideally polarized, all of these reactions must produce only negligible quantities of their products at equilibrium. The calculation of these quantities is straightforward and gives the results indicated on the right. N_K is the mole fraction of potassium in mercury, assuming a perfect solution. The first three concentrations are negligible, as demanded by the definition, but the pressure of hydrogen required for equilibrium is not. An appreciable amount of charge would therefore move from the mercury to the solution in the course of building up this equilibrium concentration.

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[5] This does not imply that the potential difference between the phases is zero, a question to be discussed below.

As a practical matter, the high hydrogen overvoltage of mercury causes the attainment of complete equilibrium to be very slow compared to the rate of attainment of ionic equilibrium within the double layer.[6] In all such cases, which are extremely common in thermodynamic practice, the slow reaction may be ignored. Occasionally the secondary effects need to be considered. Thus the current flow accompanying the process may have electrical effects of an undesired nature, or the products of the reaction may build up to significant concentrations. But these are practical matters which can be minimized by careful design.

At lower values of $|E|$ the equilibrium partial pressure of hydrogen goes down, and values of E can be found for which all of the equilibrium concentrations are negligible. At higher potentials no complications are observed in practice until $E = -2.0$ volts or thereabouts, although the equilibrium partial pressure of hydrogen is then about 10^{22} atm. The hydrogen overvoltage of mercury, of course, makes this possible.

Other slow reactions may be experienced because of imperfections of the experimental arrangement. Thus it is inconceivable that the mercurous-ion concentration could be kept down to 10^{-36} moles per liter, since the solubility of calomel allows it to rise to about 10^{-18} moles per liter. More important, particles of colloidal calomel may find their way to the surface and react according to the equation

$$Hg_2Cl_2 + 2e^- \rightarrow 2Hg + 2Cl^-$$

thus transferring charge across the interface. This reaction is again of no consequence, since it does not affect the equilibrium of the double layer.

There was a wholly erroneous opinion held at one time to the effect that the properties of the double layer at a mercury interface were fixed by the concentration of the mercurous ion (the so-called potential-determining ion). Since the latter is present at equilibrium in amounts so small as to be meaningless except in a statistical sense, and since in any case the concentration of mercurous ions will generally exceed the equilibrium value because of experimental imperfections, it should be evident that the concentration of this ion is of no importance provided it is small. The old practice of adding mercurous ions to systems to be investigated was unnecessary and escaped being harmful only because the diffusion of such ions to the interface was slow compared to the rate of establishment of equilibrium within the double layer. Those mercurous ions which reached the interface were promptly removed by electrolysis.

We may now define electrocapillarity as the study of ideal polarized electrodes and of electrodes which behave like ideal polarized electrodes. The term has sometimes been used to include the field of electrokinetics, but this practice is not recommended by the writer.

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[6] Equilibrium is attained in a matter of microseconds or milliseconds, depending upon the geometrical distribution of the electrodes (see Section IX).

The potential of an ideal polarized electrode is fixed by an external source of E.M.F., or if there be no such, then by the charge which happens to be present at the interface. In the latter case the potential of a stationary electrode will rapidly drift to that of a calomel electrode (assuming the solution is a chloride), owing to the action of colloidal calomel or other reducible matter.

If an isolated reservoir of mercury is allowed to flow in a fine stream through a deaërated solution of an inert electrolyte, it will very rapidly come to a potential of zero electronic charge (19, 53, 73). This is so because each droplet of mercury which falls carries with it a large part[7] of any residual charge which might have been present on the isolated reservoir initially. If negative ions are adsorbed on the mercury after electronic equilibrium is attained, positive ions are carried along in equivalent amounts, leaving the surface uncharged as far as electrons are concerned. Even slow-dropping mercury (3 sec. per drop) comes to a state of zero charge if oxygen and other reducible substances are very rigorously excluded (42, 61, 62). The potential of zero charge is also the potential of the electrocapillary maximum, as is well known and as we shall subsequently prove.

It was thought at one time that the potential of the isolated reservoir in the experiment described above must be identical with that of the solution, it being assumed that zero charge corresponded to zero potential difference. Such an assumption is easily proved false by comparing different solutions (84), but it is apparent anyway that zero charge does not necessarily imply zero potential difference. For example, a layer of oriented dipoles will produce a difference of potential on its two sides, although its net charge is zero. Such layers of oriented dipoles are very common,[8] and it is not at all certain that even water molecules are not oriented at a mercury surface, producing a potential difference which cannot be measured.

III. THE ELECTROCAPILLARY CURVE AND A DEFINITION OF THE POTENTIAL SCALES EMPLOYED

It has been known for a long time that the interfacial tension of mercury in an ideal polarized electrode varies with the potential difference imposed across the interface. Numerical data are given by many authors (22, 25, 54, 58, 59, 67, 68, 70, 93), the work of Gouy being the most extensive and of high accuracy (36, 38). Curves representing this variation are called electrocapillary curves, and are often almost parabolic in shape (63) (figure 1). Nevertheless one makes a serious error in assuming them to be exactly so, for the deviations from parabolic form are thermodynamically related to the interesting properties of the double layer. Because these deviations are small, other methods of obtaining the same information are more commonly employed (27, 42, 78, 79).

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[7] The capacity of the droplet relative to the solution is much greater than the self-capacity of the reservoir; hence virtually all of any excess charge accumulates on the surface of the mercury droplet.

[8] An adsorbed anion, together with a non-adsorbed cation, may be regarded as a dipole. It is in this sense that layers of oriented dipoles are most common, although layers of oriented polar molecules are also common enough.

The right-hand end of the curves in figure 1 and in all of the curves to follow corresponds to the largest negative potential imposed upon the mercury from the external source. A point corresponding to a potential more negative than the electrocapillary maximum is said to lie on the cathodic branch of the curve in question and to represent negative polarization. Potentials more positive than the electrocapillary maximum correspond to the anodic branch and represent

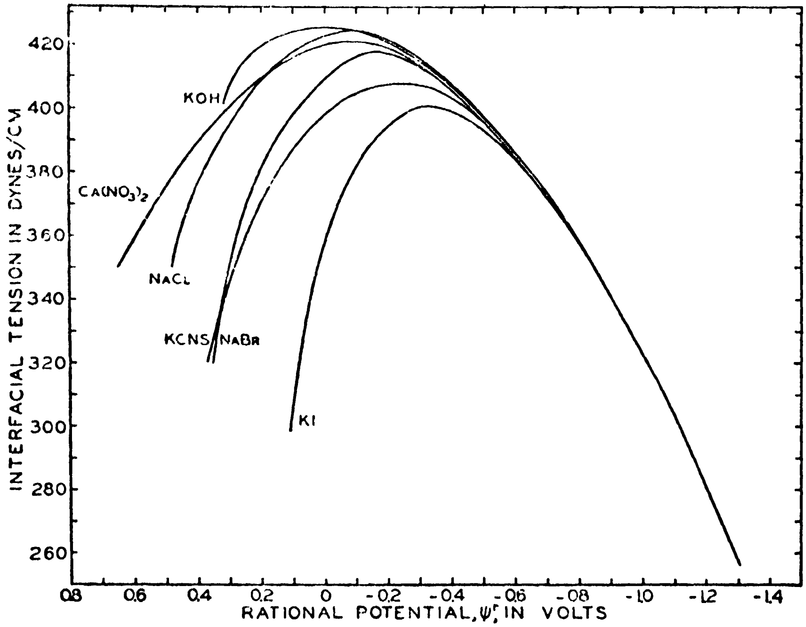

FIG. 1. Interfacial tension of mercury in contact with aqueous solutions of the salts named. $T = 18°C$. Abscissas are measured relative to a "rational" scale in which the potential difference between the mercury and a capillary-inactive electrolyte is arbitrarily set equal to zero at the electrocapillary maximum.

positive polarization. (As used by other authors, positive polarization often means that E, the observed potential, is positive.)

Until the thermodynamic theory of electrocapillarity has been discussed, there is not much to be learned from the electrocapillary curves in figure 1. There are two features of these curves worthy of remark at this point, however. The shape and position of the curves do not depend significantly upon the cation employed, except that hydronium ion and very large cations, such as tetramethylammonium ion, give somewhat different results. The differences observed with hydronium ion are probably attributable to the effects of that ion on the anions present.

Regardless of the anion present, the curves become nearly coincident on the right-hand side corresponding to negative polarization. This is understandable, since the negative charge of the mercury repels anions under these circumstances, making close contact of mercury and anion rare.

There are several kinds of electrical potential difference with which one has to deal in discussing the electrical double layer. The "absolute" or "true" potential difference between dissimilar phases is an undefined concept, and no attempt will be made to use it in this paper. The question is further discussed in Section VIII, however.

The potential of a point within a macroscopic cavity in an isotropic conductor is a definite quantity which can in principle be measured.[9] It will be called the cavity potential and is equal to what is sometimes called the electrostatic potential of the medium (1), the potential of a point "just outside" the surface. The only reason for introducing a new term is that the term "electrostatic potential" has been so often misused that it has largely lost its meaning. The term "cavity potential", on the other hand, can hardly be misunderstood.

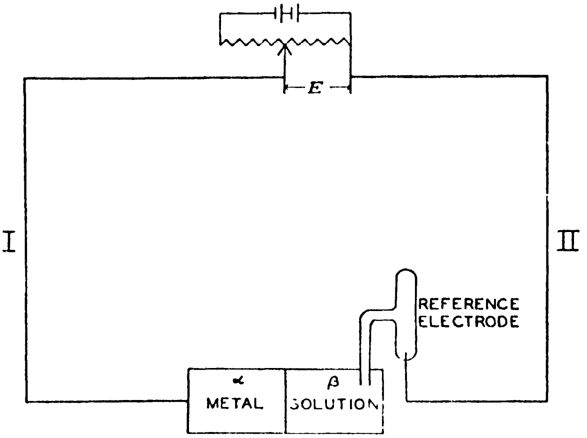

FIG. 2. Schematic representation of the system to which the equations refer

The cavity potential *difference* between metals in contact is the Volta or contact potential. It is discussed in Section VIII.

Consider the system illustrated in figure 2. I and II are wires of the same metallic substance, say copper. α is the metallic phase of an ideal polarized electrode in contact with the electrolytic solution β. The reference electrode may be supposed to contain the electrolyte β, so that liquid-junction potentials will be absent. Designating by ψ^{I}, ψ^{II}, ψ^{α}, and ψ^{β} the cavity potentials of the several phases, it is evident that

$$E + (\psi^{\alpha} - \psi^{\mathrm{I}}) + (\psi^{\beta} - \psi^{\alpha}) + (\psi^{\mathrm{II}} - \psi^{\beta}) = 0 \tag{1}$$

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[9] Actually, one can only measure differences of potential, but this is an unimportant distinction, since differences are all one ever really needs to know.

The potentiometer reading, E, is regarded as $\psi^{\mathrm{I}} - \psi^{\mathrm{II}}$. It will most often be negative in electrocapillary measurements.

In the discussions to follow, α, the metallic phase, will not be altered in composition (a more general case is discussed by Koenig (60)), so that $\psi^{\alpha} - \psi^{\mathrm{I}}$ is a constant and we may write:

$$d(\psi^{\beta} - \psi^{\alpha}) = -dE - d(\psi^{\mathrm{II}} - \psi^{\beta}) \tag{2}$$

This equation is used below in the derivation of an important thermodynamic result.

In the discussion of the *kinetic* theory of the double layer which is to be presented it is necessary to depart from the strict thermodynamic definition of potentials. Even so, it is not necessary to talk about "true" potential differences of dissimilar phases, except that liquid-junction potentials of aqueous solutions will be regarded as defined. The exact sense in which this term is used is stated in Section VIII. It is to be noted that liquid-junction potentials do not enter into the thermodynamic treatment, however.

One of the most convenient points of reference in discussing the potential difference between mercury and solutions is the potential of the electrocapillary maximum, the point of zero electronic charge. This point of reference may be determined simply and accurately by means of the mercury stream technique described in Section II. Potentials measured relative to this potential will be represented by **E**, and negative values of **E** will correspond to negative polarization. Because so many authors have spoken of the potential defined in this way as if it were at least an approximation to the "true" potential difference between the phases of an ideal polarized electrode, it is probably well to repeat that no such idea is here entertained.

Very often a normal calomel electrode is employed in measuring electrocapillary curves and the like. If the solution in question is not potassium chloride of the same concentration, this has the disadvantage of introducing liquid-junction potentials. One can eliminate the uncertainty by reporting the results in terms of **E**, the potential relative to the electrocapillary maximum. Very often one wishes to know also, however, how the potential of the electrocapillary maximum varies with concentration or from electrolyte to electrolyte. At present this information does not serve any exact thermodynamic purpose, so that the introduction of small liquid-junction potentials in this case cannot be criticized, particularly since it is unavoidable. The directly observed potential (called the electron potential in Section VIII) of the metallic phase of an ideal polarized electrode relative to the mercury in a *normal calomel electrode* connected with the solution phase of the polarized electrode will be called $\mathfrak{E}$. The connection of the calomel electrode to the solution is supposed to be made in a manner which eliminates liquid-junction potentials. In practice this means that a correction will be made as well as possible for whatever liquid-junction potentials are present.

The value of $\mathfrak{E}$ at the electrocapillary maximum of a number of electrolytes is given in column 3 of table 1. The departure from a constant value is attributed to an adsorption of anions by the mercury. From independent evidence (equation 21, *vide infra*), one knows that adsorption is small or negligible for alkali carbonates, sulfates, and hydroxides. There is also good reason to believe that alkali fluorides are not adsorbed, although the necessary data for proving this conclusively are not yet available. It is found that values of $-\mathfrak{E}^{\mathrm{MAX}}$ all lie close together in the neighborhood of 0.47–0.48 volt for these salts.

TABLE 1

Properties of the electrical double layer at the potential of the electrocapillary maximum (36, 45, 90)

ELECTROLYTE	CONCENTRATION	$\mathfrak{E}^{\mathrm{MAX}}$	ψ^{r}_{MAX}	$\Gamma^{\mathrm{MAX}}_{\mathrm{SALT}}$
	M	*volts*	*volts*	*μ coul./cm.²*
NaF	1.0	−0.472	0.008	
	0.1	−0.472	0.008	
	0.01	−0.480	0.000	
	0.001	−0.482	−0.002	
NaCl	1.0	−0.556	−0.076	3.6
	0.3	−0.524	−0.044	1.8
	0.1	−0.505	−0.025	1.1
KBr	1.0	−0.65	−0.17	10.6
	0.1	−0.58	−0.10	3.5
	0.01	−0.54	−0.06	0.6
KI	1.0	−0.82	−0.34	15.2
	0.1	−0.72	−0.24	9.1
	0.01	−0.66	−0.18	4.8
	0.001	−0.59	−0.11	1.3
NaCNS	1.0	−0.72	−0.24	14.0
	0.1	−0.62	−0.14	6.3
	0.01	−0.59	−0.11	1.3
K_2CO_3	0.5	−0.48	0.00	−2.2
NaOH	1.0	−0.48	0.00	Small
Na_2SO_4	0.5	−0.48	0.00	Small
KNO_3	1.0	−0.56	−0.08	5.5
	0.1	−0.52	−0.04	2.0
	0.01	−0.52 (?)	(?)	

The "best" value for $\mathfrak{E}^{\mathrm{MAX}}$ in the absence of adsorption of anions and cations is close to −0.480 volt.[10] If it were not for possible water orientation at the interface and unknown electrical effects at the mercury surface itself (such as an

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[10] Heretofore a value of −0.52 or −0.50 volt has been commonly used.

"overshoot" of electrons, for instance), one would possibly be justified in thinking of this as a "true" potential difference between the phases of a normal calomel electrode. What it is, rather, is the "rational" potential difference between these phases,—rational because it accounts for all the factors which are susceptible to measurement and ignores those which are neither susceptible to measurement nor significant in the interpretation of results. The rational potential difference, ψ^r, is defined by the equation:

$$\psi^r = \mathcal{E} + 0.480 \text{ volt} \tag{3}$$

It is not a thermodynamic quantity because liquid-junction potentials enter into its measurement.

There is at least one circumstance in which the rational potential must be used with care. In non-aqueous systems, the orientation of solvent molecules affects the observed potentials (23). All that can be observed is the difference between the effects of water orientation and of another solvent's orientation. Frumkin's results (23) indicate that such solvents as methanol, ethanol, and acetone are oriented with their positive (hydrocarbon) ends toward the mercury, at least more so than water. This result hardly helps one even to guess, however, how water molecules are oriented at a mercury surface, if indeed they are. Use of the rational potential as defined by equation 3 with non-aqueous systems amounts to assuming that any shifts in the value of $\mathcal{E}$ at the electrocapillary maximum in the absence of ion adsorption are to be attributed to orientation of the non-aqueous solvent molecules at the interface.

IV. THE THERMODYNAMIC THEORY OF ELECTROCAPILLARITY (23, 25, 33, 41, 46, 53, 60, 68, 77, 86, 89)

The thermodynamic theory of electrocapillarity may be derived from the Gibbs adsorption equation (Gibbs' equation 508, reference 33), according to which

$$d\sigma = -\Gamma_s dT - \Sigma\Gamma_i \, d\mu_i \tag{4}$$

In this equation σ is the interfacial tension of two immiscible phases, μ_i is the chemical potential (partial molal free energy at constant temperature and pressure) of a component X_i, Γ_i is the excess of that component, in moles per unit area of interface, over that which would be present in the system if each phase were of uniform composition, with the composition of the interior of the phase, up to a plane drawn parallel to but not necessarily coincident with the physical interface. The actual position of this plane is arbitrary except for the dictates of convenience. Curved surfaces may be considered essentially plane until the thickness of the region of inhomogeneity approaches the radius of curvature of the interface (51). The summation in equation 4 extends over all the independent components of the system, which were always thought of as neutral substances.[11] Γ_s is a quantity expressing the excess of entropy in the system in a manner exactly analogous to the definition of Γ_i. A simple but rigorous derivation of equation 4 is given by N. K. Adam (2).

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[11] This statement applies explicitly only to the derivation of Gibbs' equation 508 (our equation 4).

The adaptation of equation 4 to the problems of electrocapillarity has been subject to much dispute. The difficulty has been partly associated with a failure to understand the properties of the ideal polarized electrode, which is continually confused with non-polarizable electrodes which form the more usual subject of thermodynamic discussions of electrodes. A further difficulty has arisen because of the fact that polarized electrodes are seldom actually at equilibrium, although this is purely a practical matter and influences the experimental results almost not at all. Finally one must inquire closely into the validity of using equation 4 with charged components serving as independent components.

The early treatments of this problem are characterized by what the present writer regards as an unnecessarily obscure point of view. A typical exposition is that of Frumkin (23). The electrons are omitted from the summation and the "potential-determining" ion, Me^{+z}, the ionic component of the metallic phase, is regarded as a component of the solution, although its equilibrium concentration is vanishingly small. The potential difference between the phases is then related to the concentration of this ion, and the electronic charge is regarded as represented by an excess or deficiency of this ion at the interface. It is not surprising that this theory has not been generally endorsed, although a very careful analysis shows that it is basically correct and leads to the correct results.

An apparently rigorous treatment is given by Gouy (41), who does not employ the Gibbs adsorption theorem but proceeds from a thermodynamic analysis of the whole system, including the reference electrode and the external source of potential. The difficulty of following his analysis has apparently impeded its general acceptance, although it appears that if it were couched in modern terminology, it would be no more difficult than those treatments which employ the Gibbs equation.

A relatively simple approach is that of Koenig (60), who achieved the correct results by means of two rather improbable assumptions. He assumed, first, that equilibrium does not subsist at the interface and secondly, that there exists at the interface a barrier impermeable to charged particles. In spite of these assumptions, Koenig has given a complete and in other respects very satisfactory derivation of the equations of electrocapillarity.

Grahame and Whitney (46) have shown how it is possible to achieve Koenig's results without making his assumptions. Charged particles fail to cross the interface, not because of the presence of any barrier but because of a lack of any tendency to do so. At equilibrium, each charged particle is content to stay on its own side of the fence. The exceptions are those charged particles which react so slowly that their presence leaves the double layer virtually undisturbed.

Because of the differences in the initial assumptions, there is a slight difference in the interpretation of the symbols employed by Koenig and by Grahame and Whitney, although the equations are identical in form. In the treatment by the latter, the symbols have the same meanings as already defined for the Gibbs equation.

The basic equation, applicable to any ideal polarized electrode at constant temperature and pressure and derived from equation 4 (46 or 60), is

$$d\sigma = q\, d(\psi^{\beta} - \psi^{\alpha}) - \Sigma\Gamma_i d\mu_i \tag{5}$$

or by equation 2

$$d\sigma = -q\, dE - q\, d(\psi^{II} - \psi^{\beta}) - \Sigma\Gamma_i\, d\mu_i \tag{6}$$

where q is the surface charge density of electricity[12] on the metallic phase. Equation 6 is restricted through the use of equation 2 to systems in which the composition of the metallic phase remains unaltered.

The components of the system over which the summations in equations 5 and 6 extend are the *charged* components and the neutral molecules which do not dissociate appreciably. In principle the summation includes the components of both phases, but since we are considering that the composition of the metallic phase is to remain unaltered, the chemical potentials of the components of that phase, including the electrons, are unchanged and $d\mu_i = 0$ for each such component. Thus in effect the summation includes only the components of the non-metallic phase.

The definition of q used in the derivation of equation 5 is

$$q = -F\sum^{\beta} \Gamma_i z_i$$

where the summation is limited to the ions of the non-metallic phase. q is therefore equal to the total charge of the ions of the double layer with signs reversed. F is the Faraday. z_i is the valence of X_i, including sign.

It might appear at first sight that the value of q would depend upon the position of the surface of reference relative to which the values of Γ_i are reckoned. This is easily proved to be not so. Let the surface of reference be placed at A and let N_+^A and N_-^A be the numbers of equivalents of cations and of anions, respectively, which *would be* present in the system if the phases were uniform with the compositions of their interiors right up to the surface A. Let N_+ and N_- be the numbers of equivalents of cations and of anions which *actually are* present. Then from the definition of q

$$q = -F(N_+ - N_+^A) + F(N_- - N_-^A)$$

Because the interior of the phase is electrically neutral

$$N_+^A = N_-^A$$

and therefore

$$q = -F(N_+ - N_-)$$

This last equation shows that q does not depend upon the position of the surface of reference. If the extent of the interface is extended by 1 sq. cm., keeping the intensive variables constant, the net work required is σ and the total charge which flows through the external circuit connecting the phases is q. This makes it plain why σ and q do not depend upon the position of the surface of reference. On the other hand, the amount of one of the components which must be added to maintain the composition constant is not so unambiguously specified, since the concentration may be increased by removing appropriate amounts of the *other* components or by adding the component in question. Specifying that the surface of reference is to be fixed by setting Γ for some one component equal to zero amounts to specifying that the composition is to be adjusted, after expanding the surface, by adding or removing the other components only.

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[12] By this we mean to include only electronic charge. Adsorbed ions are explicitly excluded from the definition of q.

An interesting question arises concerning the interpretation of μ_i, the chemical potential, when the component in question is charged. This is the familiar problem of individual ionic activity coefficients, and it turns out, as always, that the particular combinations which arise in any actual experiment are determinate. As an example we may refer ahead to equation 17, where the chemical potential of the salt finally replaces the chemical potentials of the individual ionic types.

The first and simplest application of equation 6 is to an ideal polarized electrode at constant composition (designated by the subscript μ). Each term in the summation is zero, and so also is $\mathrm{d}(\psi^{\mathrm{II}} - \psi^{\beta})$. Therefore

$$(\mathrm{d}\sigma/\mathrm{d}E)_{\mu} = -q \tag{7}$$

This is the well-known Lippmann equation (67, 68). It states that the slope of the electrocapillary curve is equal to the electric charge density of the metallic surface. Experimental results verifying this and the equations to follow will be given in the next section.

It follows from equation 7 that at the potential of the electrocapillary maximum $q = 0$, as stated previously. It may be noted that the reference electrode employed in the application of equation 7 need not be one which can be joined to the solution without liquid junctions, since on the assumption merely that the liquid-junction potential does not change during an experiment carried out at constant composition,

$$\mathrm{d}E = \mathrm{d}\mathbf{E} = \mathrm{d}\psi^{r} = \mathrm{d}\mathfrak{E}$$

and equation 7 is valid regardless of the kind of potential considered. The rate of change of the slope of the electrocapillary curve is, from equation 7,

$$(\mathrm{d}^2\sigma/\mathrm{d}E^2)_{\mu} = -(\mathrm{d}q/\mathrm{d}E)_{\mu} = C \tag{8}$$

where C is the *differential capacity* of the double layer. The distinction between the differential capacity, $-\mathrm{d}q/\mathrm{d}E$, and all other kinds of capacity is of particular importance because of the fact that q is not proportional to $\mathbf{E}$. For the sake of clarity we may introduce a new type of capacity, K, designated as the static or integral capacity, and defined as

$$K = -q/\mathbf{E} \tag{9}$$

This is an appropriate definition, since $q = 0$ when $\mathbf{E} = 0$, but unlike ordinary condensers, the ratio of q to $\mathbf{E}$ in the double layer is not constant. In figure 3, showing q as a function of $\mathbf{E}$ for some typical cases, the differential capacity is the slope of the curve at a given point, but the integral capacity is the slope of the *chord* drawn from the origin to the point. Except in special cases, the differential capacity is the more significant quantity, but the integral capacity is very useful as an intermediate function in the making of calculations and as a means of representing data.

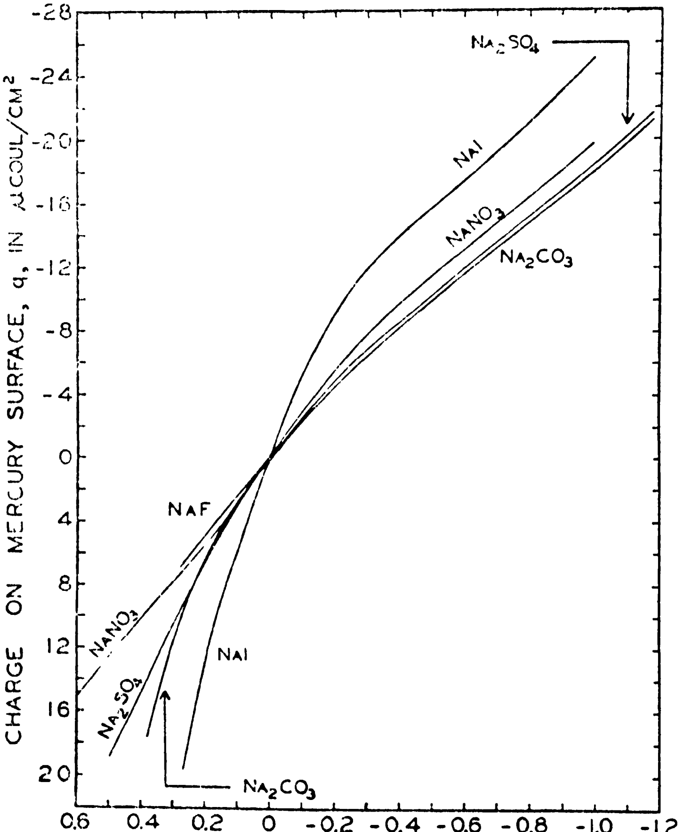

FIG. 3. Electronic charge on mercury surface in contact with uninormal aqueous solutions of the salts named. $T = 25°C$. Curves would coincide at the right if "rational" potential scale had been chosen.

If one measures the capacity of a condenser or of the electrical double layer by means of an impedance bridge, it is always the differential capacity which is obtained. Unlike ordinary condensers, the capacity of the double layer varies with the D.C. potential imposed across it. A number of plots of the differential capacity as a function of the voltage are given in the next section.

The charge q can be obtained from differential capacity curves by graphical integration, since from equation 8

$$q = -\int_0^{\mathbf{E}} C \, \mathrm{d}\mathbf{E} \tag{10}$$

The limits are as shown because $q = 0$ when $\mathbf{E} = 0$. By a further integration (of q with respect to $\mathbf{E}$) one can obtain the shape of the electrocapillary curve (equation 7), but the constant of integration cannot in this instance be ascertained other than by direct measurement of the interfacial tension at some one point.

The integral capacity is easily calculated from the differential capacity through equations 10 and 9. The differential capacity can be obtained from the integral capacity through the following equation (obtained from equations 8 and 9):

$$C = K + \mathbf{E}\left(\frac{\mathrm{d}K}{\mathrm{d}\mathbf{E}}\right)_{\mu} \tag{11}$$

It will be noted that at the electrocapillary maximum $C = K$.

We turn now to a consideration of the effects of varying the composition of the electrolyte. For these cases it becomes necessary to specify the nature of the reference electrode more closely. Liquid-junction potentials are to be avoided, which requires that the reference electrode must change as the electrolyte changes. There are two possible types of electrodes which may then be considered, those which are simply reversible to one of the anions and those which are simply reversible to one of the cations. The observed electromotive force E, *as read on the potentiometer*, will be designated by E_j^- or E_j^+ in the two types, respectively. If the reference electrode is simply reversible to one of the anions, for example, equation 6 will read:

$$\mathrm{d}\sigma = -q \, \mathrm{d}E_j^- - \Sigma \Gamma_i \mathrm{d}\mu_i - q \, \mathrm{d}(\psi^{\mathrm{II}} - \psi^{\beta}) \tag{12}$$

From this point on it will be supposed in this section that only one anionic type and one cationic type are present. The surface of reference with respect to which the Γ_i's are reckoned will be so chosen that $\Gamma_{\mathrm{SOLVENT}} = 0$. This latter choice is discussed further below. The presence of only a single anionic and a single cationic type makes the subscript j superfluous. Equation 12 now reads (if the reference electrode is reversible to the anion)

$$\mathrm{d}\sigma = -q \, \mathrm{d}E^- - \Gamma_+ \mathrm{d}\mu_+ - \Gamma_- \mathrm{d}\mu_- - q \, \mathrm{d}(\psi^{\mathrm{II}} - \psi^{\beta}) \tag{13}$$

where the + and − subscripts refer to cations and anions. From the definition of chemical potentials it follows that

$$\mathrm{d}\mu = \nu_- \mathrm{d}\mu_- + \nu_+ \mathrm{d}\mu_+ \tag{14}$$

where μ is the chemical potential of the neutral salt and ν_+ and ν_- are the numbers of cations and anions, respectively, formed by the dissociation of one molecule of salt.

The potential $\psi^{\mathrm{II}} - \psi^{\beta}$ varies with the chemical potential of the anion, if the reference electrode is simply reversible to the anion, according to the equation

$$z_-F\,\mathrm{d}(\psi^{\mathrm{II}} - \psi^{\beta}) = \mathrm{d}\mu_- \tag{15}$$

From the definition of q (or from the electroneutrality requirement)

$$q + z_+\Gamma_+F + z_-\Gamma_-F = 0 \tag{16}$$

When equations 14, 15, and 16 are introduced into equation 13, and noting that $z_+/z_- = -\nu_-/\nu_+$, the following simple and important result is obtained:

$$\mathrm{d}\sigma = -q\,\mathrm{d}E^- - \frac{\Gamma_+}{\nu_+}\,\mathrm{d}\mu \tag{17}$$

If the reference electrode is reversible to the cation, one obtains by an exactly analogous procedure:

$$\mathrm{d}\sigma = -q\,\mathrm{d}E^+ - \frac{\Gamma_-}{\nu_-}\,\mathrm{d}\mu \tag{18}$$

These equations and also those which follow may be put in forms more suitable for computation by the introduction of the relation

$$\mathrm{d}\mu = \nu RT\,\mathrm{d}\ln\{m\gamma(\nu_+^{\nu_+}\nu_-^{\nu_-})^{1/\nu}\} = \nu RT\,\mathrm{d}\ln m_{\pm}\gamma = \nu RT\,\mathrm{d}\ln m\gamma \tag{19}$$

The nomenclature is essentially that of Lewis and Randall. γ is the mean activity coefficient, m is the molality, and $m_{\pm}$ is the mean molality, defined by the relation $m_{\pm} = m(\nu_+^{\nu_+}\nu_-^{\nu_-})^{1/\nu}$. ν is the sum of ν_+ and ν_-.

At constant composition equations 17 and 18 reduce to the Lippmann equation. At the electrocapillary maximum, where $q = 0$, one has

$$\mathrm{d}\sigma^{\mathrm{MAX}}/\mathrm{d}\mu = -\,\Gamma_+^{\mathrm{MAX}}/\nu_+ = -\,\Gamma_-^{\mathrm{MAX}}/\nu_- \tag{20}$$

The symbol $\mathrm{d}\sigma^{\mathrm{MAX}}/\mathrm{d}\mu$ means that the differentiation occurs at $q = 0$.

The quantities on the right are equal to $\Gamma_{\mathrm{SALT}}^{\mathrm{MAX}}$, the number of moles of neutral salt adsorbed per unit area of interface at the electrocapillary maximum. Therefore

$$\mathrm{d}\sigma^{\mathrm{MAX}}/\mathrm{d}\mu = -\,\Gamma_{\mathrm{SALT}}^{\mathrm{MAX}} \tag{21}$$

Values of $\Gamma_{\mathrm{SALT}}^{\mathrm{MAX}}$ computed from this equation are listed in table 1. Unfortunately the accuracy with which σ^{MAX} can be ascertained is not as great as one would wish for this purpose. The equation itself, however, suffers from no known restrictions other than those appropriate to the Gibbs adsorption equation itself.

At constant E^- or E^+ equations 16 and 17 give

$$-\,\nu_+(\mathrm{d}\sigma/\mathrm{d}\mu)_{E^-} = \Gamma_+ \text{ and } -\,\nu_-(\mathrm{d}\sigma/\mathrm{d}\mu)_{E^+} = \Gamma_- \tag{22}$$

These results indicate that Γ_+ or Γ_- can be obtained at any point on the electrocapillary curve by measuring the rate of change of interfacial tension with composition at constant imposed potential, E^+ or E^-. (The potentiometer reading is the thing to be held constant, not any ill-defined quantity.) It has not been very generally realized that Γ_+ and Γ_- could be calculated separately without the introduction of non-thermodynamic assumptions. Some results obtained with these equations will be presented in the next section.

Very convenient alternate forms of equation 22 are obtained by dividing through by equation 7 (with E^- or E^+ for E)

$$-\nu_+ q(\mathrm{d}E^-/\mathrm{d}\mu)_\sigma = \Gamma_+ \tag{23}$$

and

$$-\nu_- q(\mathrm{d}E^+/\mathrm{d}\mu)_\sigma = \Gamma_- \tag{24}$$

In obtaining these results the identity $(\mathrm{d}\sigma/\mathrm{d}\mu)_E(\mathrm{d}\mu/\mathrm{d}E)_\sigma(\mathrm{d}E/\mathrm{d}\sigma)_\mu = -1$ has been used. Differentiation of equation 22 gives:

$$-\nu_+(\partial^2\sigma/\partial\mu\partial E^-) = \partial\Gamma_+/\partial E^- \text{ and } -\nu_-(\partial^2\sigma/\partial\mu\partial E^+) = \partial\Gamma_-/\partial E^+ \tag{25}$$

Since the order of differentiation is immaterial, the left-hand members may be rewritten, with the aid of the Lippmann equation (7), as

$$\nu_+(\mathrm{d}q/\mathrm{d}\mu)_{E^-} = (\mathrm{d}\Gamma_+/\mathrm{d}E^-)_\mu \text{ and } \nu_-(\mathrm{d}q/\mathrm{d}\mu)_{E^+} = (\mathrm{d}\Gamma_-/\mathrm{d}E^+)_\mu \qquad (26)^{13}$$

Graphical integration of the left-hand members of these equations with respect to E^- or E^+ gives $\Gamma_\pm$ as a function of $E^\mp$ except for the constant of integration. Since q can be obtained from capacity data (equation 10), Γ_+ and Γ_- can be obtained from capacity data, except for the constant of integration. The latter can be evaluated through the use of equation 20 or 21, but this requires accurate interfacial tension data which may not be available. Alternative methods of fair accuracy but not of strictly thermodynamic character will be discussed later.

The evaluation of Γ_+ and Γ_- for electrocapillary systems of many kinds is an important task so far barely begun. The chief difficulty has been the lack of accurate experimental data and unclear ideas concerning the meaning of the thermodynamic equations.

We may now consider the reasons for the assumption made earlier that $\Gamma_{\mathrm{SOLVENT}} = 0$. Basically, the justification is that of simplicity. The equations take their simplest form when this assumption is made. But nothing is lost thereby, since it is only a stoichiometric calculation to find the amount by which any Γ changes for a shift in the position of the surface of reference through a given distance. Moreover, this is all the information which can be obtained by thermodynamic means, since if one chooses to set $\Gamma_{\mathrm{M}_0{}^+} = 0$, the only convenient alternative, one obtains equations having exactly the same physical significance.[14]

As a matter of convenience, Γ_+ and Γ_- will frequently be expressed in units of charge per unit area in spite of the fact that their definitions are in terms of moles per unit area. It is believed that this inconsistency will cause no confusion.

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[13] These equations could have been obtained by inspection from equations 17 and 18 by noting that $\mathrm{d}\sigma$ is an exact differential. Equations 26 are the reciprocity relations satisfied by the line integral of an exact differential.

[14] More explicitly, one obtains the equations given by Koenig (60). An example will serve to illustrate the truth of the assertion that these equations are equivalent to those here derived. Instead of our equation 21, Koenig gives

$$\frac{\mathrm{d}\sigma^{\mathrm{MAX}}}{\mathrm{d}\mu} = -\Gamma^{\mathrm{MAX}}_{\mathrm{SALT}} + \frac{\mathrm{N}^\beta}{\mathrm{N}_0}\Gamma_{\mathrm{SOLVENT}}$$

V. VERIFICATION AND APPLICATION OF THE THERMODYNAMIC THEORY OF ELECTROCAPILLARITY

The two principal kinds of equations developed in the thermodynamic theory of electrocapillarity are those which deal with variations of electrical potential and those which deal with changes of composition. The first class has been extensively verified, the second not at all. There is no serious doubt about the correctness of either class, however.

A three-way check of the first class of equations is shown in figure 4. For convenience the integral capacity is plotted. The three types of points represent (*a*) an evaluation of K from differential capacity data using equation 10, (*b*) an evaluation of K from interfacial tension data using equation 7, and (*c*) an evaluation of q from direct measurements of the charge carried by falling mercury droplets of known surface area. In the case cited, all three types of data were known with exceptional accuracy. There are no arbitrary constants in these data. Other verifications of the first class of equations are given by Frumkin (23), by Proskurnin and Frumkin (78), by Borissova and Proskurnin (9), by Craxford (14), and by Grahame (42). Proskurnin and Frumkin pointed

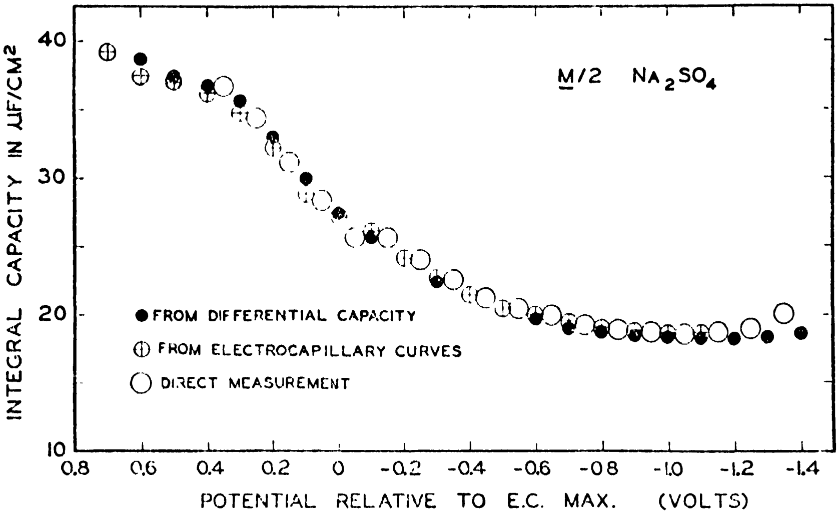

FIG. 4. Three-way check of the Lippmann equation. Crossed circles computed from data by Gouy (36).

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where N_0 is the mole fraction of solvent and N^β is the mole fraction of solute within the solution. But this equation can be derived from equation 21, for if $\Gamma_{\text{SOLVENT}} = y$ at some arbitrarily chosen interface and zero at the interface to which equation 21 refers, then $\Gamma_{\text{SALT}}^{\text{MAX}}$ will change by exactly $N^\beta y/N_0$ when the surface of reference is moved from one position to the other. When this is added to equation 21, Koenig's equation results. It is to be noted that $d\sigma^{\text{MAX}}/d\mu$ has a fixed value independent of the position of the surface of reference.

out in 1935 (78) that contamination of the metallic surface by traces of capillary-active substances had rendered earlier measurements of the differential capacity so inaccurate that the demands of equation 8 had seemed not to be satisfied. This difficulty is overcome nowadays either by extraordinary care in the purification of solutions and metallic surfaces (9) or by the use of a dropping electrode technique (42, 43).

Differential capacity data for representative types of the solutions which have been investigated are given in figures 5–6.[15] Other data of the same kind are given by Gouy (36), by the Russian group of workers (9, 27, 78, 87, 88), and by Grahame (42, 43).

The characteristics of the differential capacity curves in figures 5–6 depend very greatly upon the anion and almost not at all upon the cation, except the hydronium ion, provided it is of fairly low molecular weight. This was to be expected, of course, from the fact that the electrocapillary curves show such behavior. An explanation of many of the characteristics of these curves will be evident from the mathematical development of the kinetic theory to follow, although not all of the details are fully understood. For instance, there is still some difficulty in explaining the difference between the behavior of hydroxides and fluorides under negative polarization, since both of these anions have large hydration energies (7) and would be expected to be as much alike as two univalent cations. The "humps" which appear near the electrocapillary maximum of most curves are not correctly predicted by any theory and are believed by the present author to arise from the mutual electrostatic repulsion of ions in the double layer in directions parallel to the interface.

The second type of thermodynamic equation of electrocapillarity deals with the effects of varying the composition. In figure 7 there are presented data by Gouy on the interfacial tension at the electrocapillary maximum of several electrolytes (36). Many more data are contained in the original paper. According to equation 21, the slope of these curves measures the amount of electrolyte adsorbed at the interface. Values calculated in this way are included in table 1. There has been no experimental verification of these results by independent means, although such verification is theoretically possible. There is no real doubt, however, concerning the validity of the equation from which they are derived.

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[15] These data by the author disagree somewhat with similar data by Vorsina and Frumkin (87, 88). The disagreement is not serious except at small negative values of **E** with dilute solutions. In plots of q *vs.* **E** one observes two roughly linear regions connected by a nonlinear region near **E** = 0 (6; 10, p. 74; 13, 76). Since the slope of these curves gives the differential capacity, the impression has grown up that there are two "characteristic" values of capacity corresponding to positive and negative polarization, respectively. This impression is not borne out by the differential capacity curves themselves, which do not approach a constant value over any considerable range of potentials with positive polarization. The appearance of the q *vs.* **E** curves is somewhat misleading, since very considerable changes of slope may go unnoticed or pass as experimental error. Even with negative polarization the differential capacity does not approach a constant value but has a flat minimum.

Values of $\Gamma^{\mathrm{MAX}}_{\mathrm{SALT}}$ have been plotted against ψ^{r}_{MAX} in figure 8. A few discordant values have been omitted (0.01 *M* sodium thiocyanate; 0.1 *M* sodium chloride; 0.1 *M* potassium nitrate). Except for the omitted points, the curves at a given concentration are consistent enough to serve as a starting point for estimating $\Gamma^{\mathrm{MAX}}_{\mathrm{SALT}}$ from ψ^{r}_{MAX}. The latter is so much easier to measure that in many instances

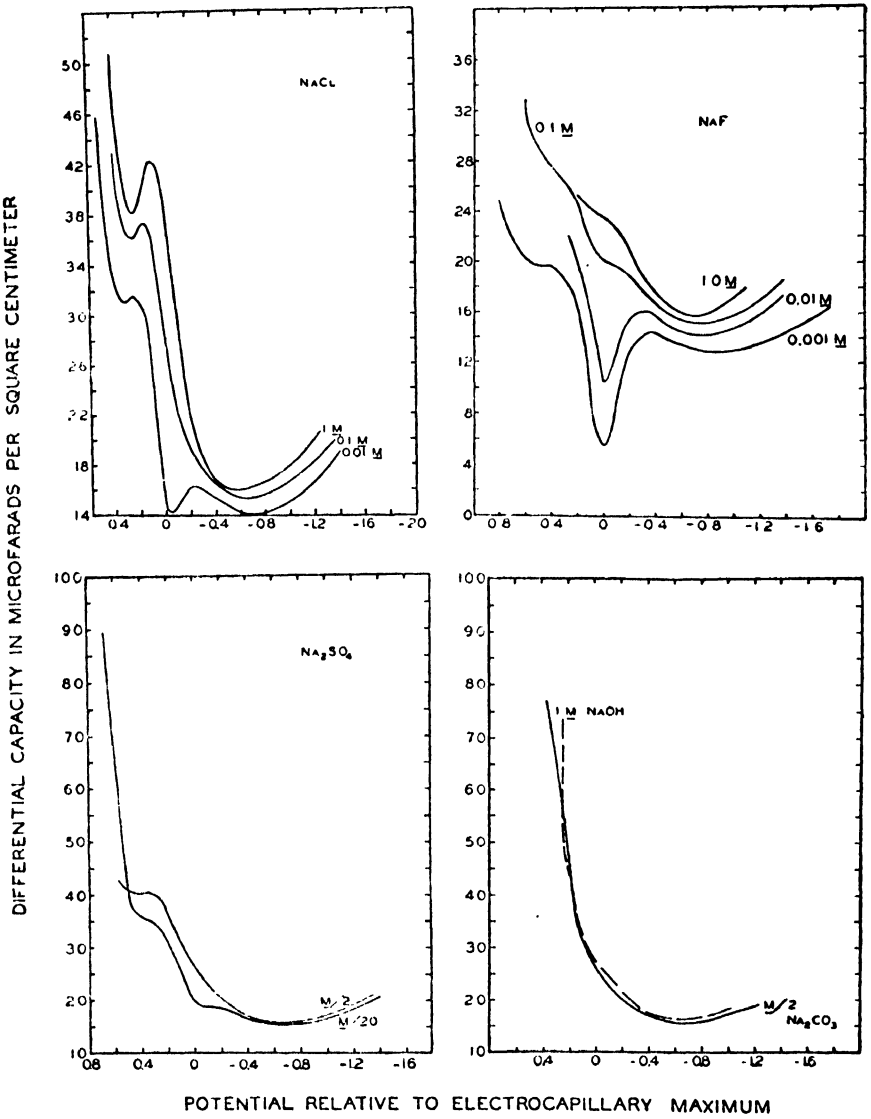

FIG. 5. Differential capacity of the electrical double layer between mercury and aqueous solutions of the salts named. $T = 25°\mathrm{C}$.

the values taken from the curve are likely to be more accurate than the measured values. Thus for 0.01 *M* sodium thiocyanate and 0.1 *M* sodium chloride the

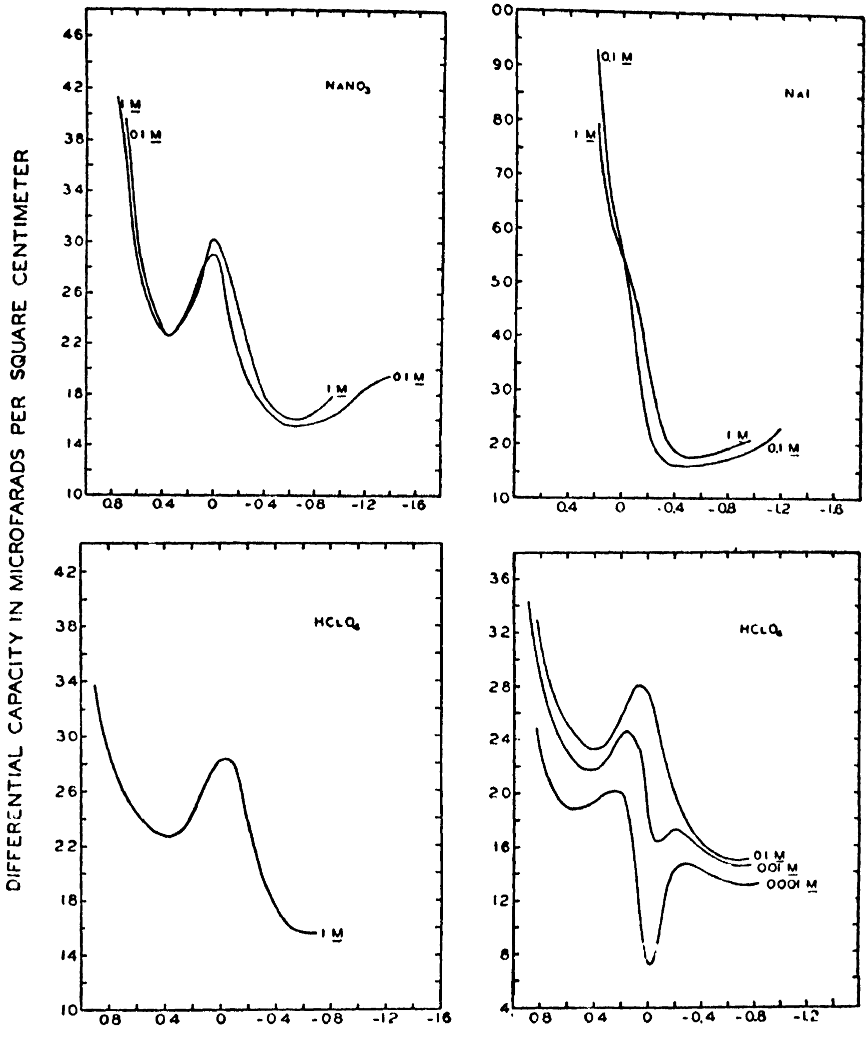

FIG. 6. Differential capacity of the electrical double layer between mercury and aqueous solutions of the salts named. $T = 25°C$.

observed values are probably in error. On the other hand, all of the observed values for nitrates are a little higher than the curve would suggest, a result which is correlated with the dissimilarity of the cathodic branches of the differential capacity curves of halides and nitrates.

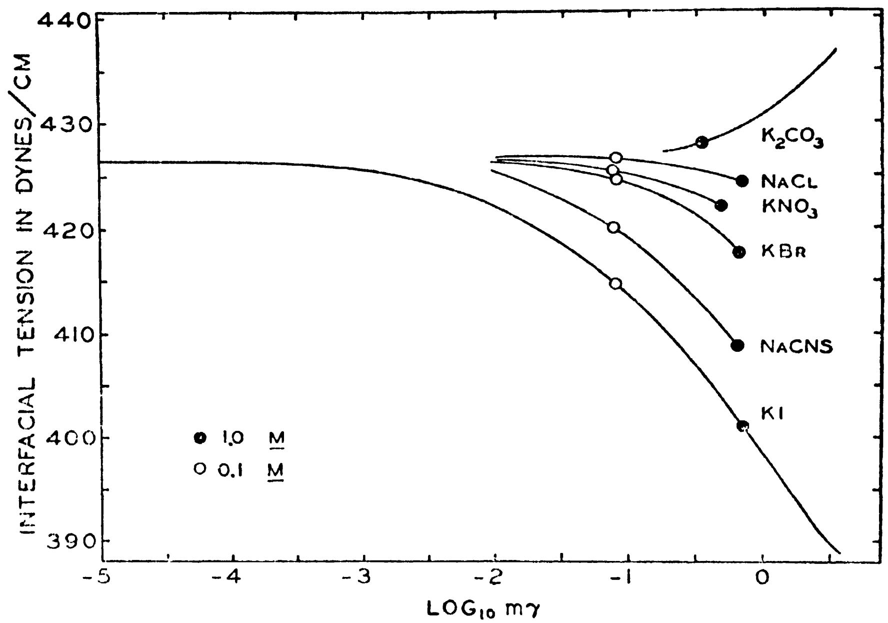

FIG. 7. Maximum interfacial tension of mercury in contact with aqueous solutions c the salts named $T = 18°C$. Data by Gouy (36). The slope measures the amount of sal adsorbed (equations 19 and 21). (Additional points not shown were used in the construc tion of the figure.)

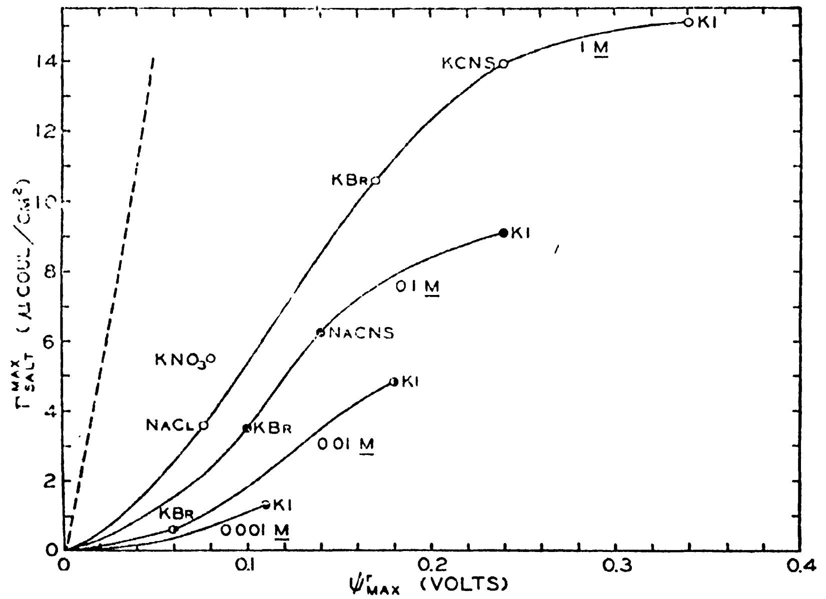

FIG. 8. Salt adsorption on a mercury surface at the potential of the electrocapillary maximum. Lines connect points of same concentration. Ordinates represent shift of the potential of the electrocapillary maximum caused by the salt. The dotted line shows calculated values for unimolar solutions based upon the erroneous assumption that $\psi^o = \psi^i$.

Curves of Γ_+ *vs.* E^- can be obtained in two ways, through equation 22[16] or through equation 26. In the latter case only the shape of the curve is ascertained, the constant of integration being unknown. If the curves are made to coincide at one point, the agreement at other points constitutes a partial check on the validity of equations 22 and 26. Such a check is shown in figure 9,

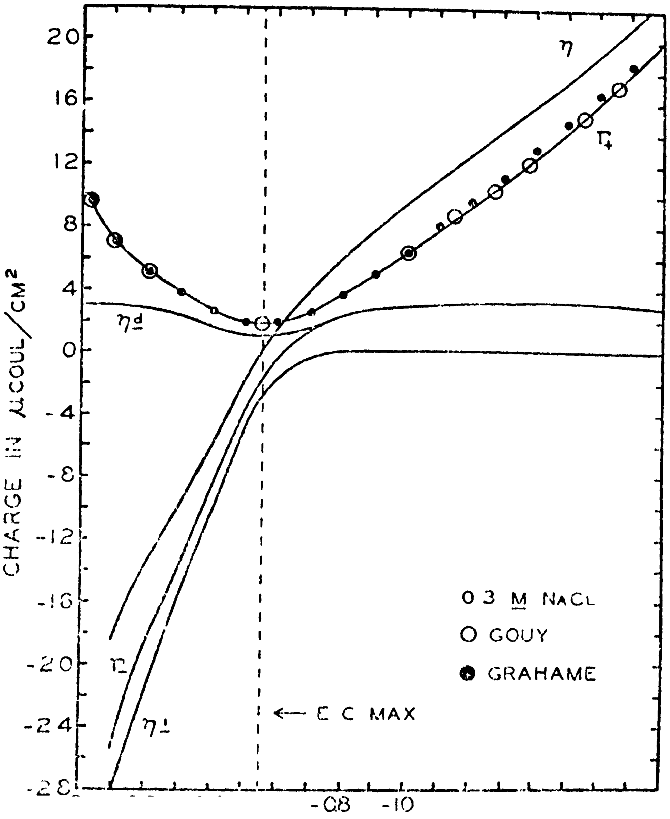

FIG. 9. Components of charge of the double layer between mercury and aqueous 0.3 *M* sodium chloride solution. $T = 25°C$. Open circles computed from data by Gouy (36). η is total charge. Γ_+ is charge attributable to cations in the double layer; η^d_- is charge attributable to anions repelled from the diffuse double layer; η^i_- is charge attributable to anions adsorbed on mercury surface. Γ_- is the sum of these two. Potentials measured relative to 0.3 *M* sodium chloride–calomel electrode.

where Γ_+ (expressed in μ coul./cm.^{2}) has been calculated for 0.3 *M* aqueous sodium chloride by means of each of the two equations mentioned. The agreement obtained has more to do with the accuracy of the experiments than with the accuracy of the equations, however, since equation 26 is derived from equation

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[16] Other values of Γ_+ and Γ_- obtained through the use of equation 22 are given by Iofa, Frumkin, Ustinskii, and Elman (54, 55).

22. Again it would be possible to verify these results by direct analytical means,[17] but such verification has not been attempted.[18]

In figure 9 there are also plotted Γ_- and $-q$ (labeled η in conformity with the nomenclature of the next section) obtained from equations 26 and 10, respectively, and also two other quantities, η_-^i and η_-^d, to be defined later. These are components of Γ_- and are obtained by non-thermodynamic means as explained below.

Figure 10 gives similar data for another concentration of sodium chloride. These data are not of the highest possible accuracy, and will probably need some revision when recently discovered techniques (43, 79) have been more widely applied.

Γ_+ shows the interesting property of being positive even on positive polarization. On positive polarization, the mercury surface holds anions not only by coulombic forces but also by covalent bonding. The resulting binding is known as a specific adsorption because it is specific to the various anions. As a result of specific adsorption, more anions are held on the mercury surface than corresponds to the positive charge on the mercury. Consequently the net charge of the two layers is negative and cations are attracted. The specific adsorption observed at the electrocapillary maximum is only a special case of this phenomenon.

We turn now to the application of the above results to problems which cannot be settled by thermodynamic means alone. The assumptions we are about to make are in better agreement with the experimental data than any others of which we know. Part of the evidence has been given by Whitney and Grahame (90) and is repeated in Section VI in somewhat different form.

Ions which are held to the mercury surface by covalent bonds are certainly not separated from the surface of the metal by water molecules. Ions which are held to the mercury surface by van der Waals forces are also assumed not to be separated from the surface by solvent molecules. Ions which are *not* held to the mercury surface by covalent bonds or by van der Waals forces will be assumed to be separated from that surface by a solvent sheath, at least when the solvent is water. This amounts to assuming that the work needed to displace the solvent on the side of the ion nearest the interface is not negligible compared to the work needed to move the ion up to the nearest point of approach not involving such solvent displacement. The locus of the electrical centers of a layer of adsorbed ions, whether adsorbed by covalent bonds or van der Waals forces or both, will be called the *inner* Helmholtz plane. The locus of the electrical centers of hydrated or solvated ions in contact with the mercury surface will be called the *outer* Helmholtz plane. It is assumed that the *outer* Helmholtz plane is the same for all ions, even for anions, although the latter are generally more easily dehydrated. It should be noted that we do not speak of a *layer* of ions at the outer Helmholtz plane, since the forces which act there are long-range forces and serve only to produce an ionic atmosphere. Except in the case of very large adsorbed ions, it is to be expected that the outer Helmholtz plane will lie farther from the surface than the inner.

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[17] One could allow a stream of mercury to flow through a column of solution while maintaining the potential at a fixed value and measuring the current flow and the time. An analysis of the top and bottom "compartments" would give the amount of neutral salt transferred. Knowing the integral capacity as a function of E, one could compute q and therefore the area of the mercury surface. From the total charge transferred and the known transference numbers, one could then compute the amounts of each ion moved from one compartment to the other by transference. These data would be sufficient to determine Γ_+ and Γ_-. The difficulty, of course, lies in the difficulty of avoiding convection currents during the experiment. The experiment is interesting primarily in that it shows that Γ_+ and Γ_- are measurable magnitudes apart from considerations of interfacial tension.

[18] Such measurements as have been made have been done with non-polarized electrodes (66, 74, 75, 83).

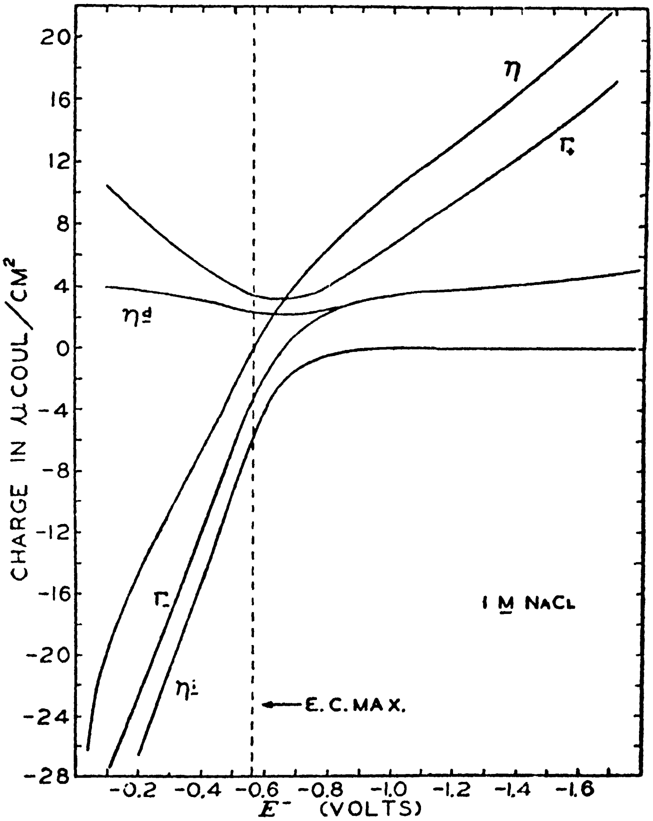

FIG. 10. Components of charge of the double layer between mercury and aqueous 1 *M* sodium chloride solutions. T = 25°C. See legend of figure 9. Potentials measured relative to 1.0 *M* sodium chloride–calomel electrode.

The great similarity of the electrocapillary properties of low-molecular-weight cations leads one to believe that they do not populate the inner Helmholtz plane, where their various radii would lead to varying results. If this conclusion be accepted (and additional evidence for it will be presented at the end of Section VI), it follows that Γ_+ is determined solely by the condition of the double layer from the outer Helmholtz plane out into the solution. Therefore if one compares two points having the same value of Γ_+ on a curve such as that in figure 9, one expects that the potential of the outer Helmholtz plane will be the same in the two cases and that a "map" of the double layer showing concentrations and potentials would be the same for the two cases from this point out. Moreover, even on comparing different solutions of the same valence type and of the same concentration, if the cation is the same or behaves the same, the difference of anion should make little difference, and a "map" of the double layer for a condition corresponding to the same value of Γ_+ should be the same for both. This principle will be subject to experimental verification when more data of sufficient accuracy became available. Meanwhile it may be used as a guide in the absence of such information.

The differential capacity of the region between the mercury surface and the inner Helmholtz plane will be designated as C^i and defined by the equation

$$C^i = \mathrm{d}q/\mathrm{d}(\psi^r - \psi^i) \tag{27}$$

ψ^i is the potential of the inner Helmholtz plane. Its meaning is discussed in Section VII. The integral capacity of this region will be designated by K^i and defined by the equation

$$K^i = q/(\psi^r - \psi^i) \tag{28}$$

From these two equations it follows that[18a]

$$K^i = \frac{1}{\psi^r - \psi^i} \int_0^{\psi^r - \psi^i} C^i \, \mathrm{d}(\psi^r - \psi^i) \tag{29}$$

This equation is used below for the evaluation of K^i.

The potential at which Γ_+ is a minimum, the Γ_+^{MIN}-potential, is one of special interest.[19] At this point a small change in the imposed over-all potential causes no change in the value of Γ_+ and therefore no change in the potential of the outer Helmholtz plane, ψ^o. The potential of the inner Helmholtz plane, ψ^i, must also remain unchanged, since it controls ψ^o. Therefore the differential capacity of the whole double layer is equal to the differential capacity of the region between the mercury surface and the inner Helmholtz plane, C^i. This capacity is nearly the same at the Γ_+^{MIN}-potentials of each of the sodium chloride concentrations studied. It lies between 32 and 34 μf/cm.^{2} and its constancy leads one to suppose that it is constant under a wide range of conditions. If it is constant, it follows from equation 29 that it is equal to the integral capacity of the same region. Thus

$$C^i = K^i \tag{30}$$

[18a] The limits of integration are set by noting from elementary electrostatics that when $q = 0$, $\psi^r = \psi^i$.

[19] Note that Γ_+^{MIN} is the minimum value of Γ_+, whereas Γ_+^{MAX} is the value of Γ_+ at the electrocapillary maximum. The subscript or superscript MAX always refers to the electrocapillary maximum in this paper.

This equation is important in that it gives a means of calculating K^i and therefore ψ^i, the potential of the inner Helmholtz plane, from experimentally observable results. The results will be accurate near the Γ_+^{MIN}-potential and probably also elsewhere.

Equation 28 is one of the Stern equations (85), of which we shall speak later. There is one important difference, however, in that ψ^i is not here regarded as identical with ψ^o. Stern recognized the desirability of distinguishing between these quantities, but underestimated the necessity for doing so. At the electrocapillary maximum of 0.3 M sodium chloride, for instance, $\psi^i = -0.011$ volt, whereas $\psi^o = -0.022$ volt according to a later estimate which is probably not greatly in error.

It is evident from figures 9 and 10 that the adsorptive forces are becoming stronger as the mercury becomes more highly charged positively.[20] It has not always been recognized that this is not simply the result of an increased coulombic attraction in a simple sense but represents a strengthening of the covalent bond by which the anions are held to the mercury surface. This result is to be expected on any theory of chemical binding. The positive charge enhances the stability of the electron-pair which binds the atoms. This same phenomenon is apparent in the chemical behavior of simple inorganic salts. When two such salts are compared, differing only in the charge on the cation, the more highly charged cation binds the anions much more strongly. Comparing ferrous and ferric chlorides, for instance, the latter dissociates much less than one would anticipate from interionic attraction theory. Ferrous and ferric hydroxides display the same behavior, the greater insolubility of the latter corresponding to far greater bond strength. Salts of tin, lead, mercury, manganese, and cobalt exhibit this behavior in marked degree. Salts of copper appear to constitute an exception, for which some reason can perhaps be found. The nitrates, perchlorates, and bisulfates of the metals do not show the phenomenon, no doubt because these ions are not bound to metallic ions by covalent bonds to any marked extent. It is interesting to note that nitrate, perchlorate, and bisulfate ions show little or no specific adsorption on mercury of the type associated with covalent-bond formation until the mercury is strongly positively charged. The fluoride ion, which behaves differently from all of these ions, is probably unique because its strong electronegativity hinders the formation of covalent bonds with cations to a large degree.

It would be desirable to be able to set down rigid rules for the experimental recognition of the presence or absence of adsorption of ions. This we cannot do in general, since the concept is not a purely thermodynamic one. Certain nonthermodynamic considerations are possible, however. We restrict our attention first to the electrocapillary maximum.

One is tempted to say that if $\Gamma_{\text{SALT}}^{\text{MAX}} = 0$ at the electrocapillary maximum, ion adsorption is absent, and this is nearly true. But it is found that in very concentrated solutions of salts whose ions are believed to be unadsorbed, $\Gamma^{\text{MAX}}_{\text{SALT}}$ becomes negative (table 1 or figure 7). This effect may be thought of as being caused by a small constant adsorption of solvent which results in the displacement of larger amounts of solute in concentrated than in dilute solutions. Other explanations which could be given are essentially equivalent to this. Because of this effect, $\Gamma^{\text{MAX}}_{\text{SALT}}$ is negative in the absence of ionic adsorption. Positive values of $\Gamma^{\text{MAX}}_{\text{SALT}}$ indicate adsorption, but zero or negative values do not guarantee its absence.

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[20] The increasing values of Γ_+ show this, since Γ_+ would not even be positive if adsorptive forces were absent. The calculations leading to figure 15 (see Section VII) give a quantitative measure of the effect.

At potentials different from that of the electrocapillary maximum, the situation is likewise complicated. If Γ_+ is positive on positive polarization, anion adsorption is indicated. If Γ_- is negative on negative polarization, cation adsorption is indicated. If Γ_+ is negative on positive polarization, anion adsorption is probably absent. If Γ_- is positive on negative polarization, cation adsorption is probably absent.

When more data are available for capillary-inactive electrolytes such as sodium fluoride, it will probably be possible to say with more exactitude what Γ_+ and Γ_- must be in any given case if adsorption is to be deemed absent.

The term "*specific* adsorption" is used in cases where it seems probable that covalent-bond formation is responsible for an observed adsorption. Otherwise the less explicit term "adsorption" is used. Iodide ion is almost certainly held to the mercury surface by covalent bonds, an effect which also limits the ionizability of mercurous and mercuric iodides. There is a considerable correlation between the specific adsorbability of anions on mercury and the ionizability (or solubility) of the corresponding mercury salts, but because of the exceptions and special cases, this correlation cannot be made very convincing without extensive discussion. The nitrates constitute the most glaring discrepancy, since nitrate ion shows greater adsorbability than chloride ion. van der Waals (dispersion) forces suggest themselves at once in this and similar cases (e.g., perchlorates), but the situation is by no means clear.

VI. THE KINETIC THEORY OF THE DIFFUSE DOUBLE LAYER (8, 11, 16, 20, 21, 39, 40, 72)

The kinetic theory of the diffuse double layer deals with that part of the double layer which lies at or beyond the outer Helmholtz plane. At distances closer to the interface than this, the assumptions break down and other methods of treatment are necessary. These other methods are discussed in the next section.

There are three equations upon which the theory to be developed rests, and since it is possible to proceed from these without further approximations or assumptions directly to experimentally significant results, it is evident that any faults in the theory must be faults of the original equations. The three equations to which we refer are: (*1*) the Poisson equation for a system whose potential varies in only one direction

$$d^2\psi/dx^2 = -4\pi\rho/DD_0 \tag{31}$$

(*2*) the Boltzmann equation

$$n_i = n_{0i}e^{-w_i/kT} \tag{32}$$

and (*3*) an equation expressing the work w_i needed to bring an ion of type X_i from the interior of the solution to the point in question:

$$w_i = z_i\epsilon\psi \tag{33}$$

In these equations ψ is the electrical potential (relative to the interior of the solution) at a point within the double layer (discussed below); ρ is the electric density (charge per unit volume) at the point in question; x is the distance of this point from the surface of discontinuity, positive values of x corresponding to points within the solution; D is the dielectric constant of the solution; D_0 is 4π times the permittivity of free space (discussed below); n_i is the number of ions of type X_i per unit of volume at a point whose potential is such that an amount of work w_i is needed to bring an ion of this type from the interior of the solution to the point in question; n_{0i} is the number of ions of type X_i per unit of volume within the body of the solution; k is the Boltzmann constant; T is the absolute temperature; z_i is the valence number including sign; and $z_i\epsilon$ is the charge of an ion X_i. Most of these quantities call for further comment.

The potential at a point within the double layer is not a wholly unambiguous quantity, particularly when the "point" in question is really a region as large as the solvated ion. For the present the best solution to the difficulty is to regard equation 33 as a definition of ψ. This procedure is not a complete solution to the problem, however, for it assumes that all of the work w_i is electrical work, and it assumes that the same value of ψ will be obtained whatever ion is used for the test ion. The other kinds of work neglected by this procedure are (*1*) the work involved in displacing polar solvent molecules from a region of high field strength (8), (*2*) the work involved in pushing all of the other ions in the region a little closer together (the crowding effect), and (*3*) the work involved in distorting or displacing the solvent sheath of a solvated ion as a result of a too close approach of the ion to the metallic surface. The first-named effect is almost certainly very small compared to other errors in the theory. The second effect has been considered in a quantitative manner by Bikerman (8), but it is unfortunately true that the introduction of factors intended to account for this effect in the fundamental equations leads to a differential equation which cannot be integrated without assuming that the potential is very small, so small that the results have a very limited range of validity. Within this range, however, the crowding effect is almost certainly of minor consequence. Even if the mathematical difficulties could be overcome, it is still not certain how the effects of crowding should be introduced. One may treat the problem as a volume effect, the ions having a lesser probability of entering a region already partly filled, or one may treat the problem as an electrostatic effect, computing the work required to make a place for the test ion. Both types of calculation are subject to great uncertainties. It will be shown presently that the double layer is not more crowded than a moderately concentrated solution, so that the error introduced by the neglect of crowding is probably not so serious as to make the entire treatment fictitious. Nevertheless, the neglect of crowding is likely to prove to be the most serious defect of the kinetic theories of the diffuse double layer now in vogue.

The third effect listed above, the work required to displace the solvent sheath of an ion on the side of the metallic phase, is certainly not small enough to justify its neglect in aqueous solutions.[21] The equations to be developed in this section may not be applied, therefore, to ions whose centers lie closer to the interface than the outer Helmholtz plane. This is a point which has sometimes been overlooked or ignored.

The dielectric constant D is dimensionless. We shall use the value 78.49 for water at 25°C. (17). The propriety of using the dielectric constant of the solvent in equation 31 and in the equations to be derived from it is discussed below.

The constant D_0 is introduced in order to avoid the confusion which accompanies attempts to make the dielectric constant other than a dimensionless constant. A discussion of this problem is given by Wood (94) and also by Guggenheim (50). D_0 may be defined by the equation

$$f = \frac{q_1 q_2}{r^2 D_0}$$

where f is the force acting between charges q_1 and q_2 *in a vacuum* at a distance r. In practical units D_0 has the value $10^9/c^2 = 1.112 \times 10^{12}$ coul.-volt^{-1}-cm.$^{-1}$ A similar quantity, κ_0, called the permittivity of free space, has been introduced by Harnwell (52), who gives a clear discussion of the reasons for the introduction of such a constant. We have chosen to introduce D_0, equal to $4\pi\kappa_0$, in order to make our equations more closely resemble those which have appeared in previous treatments of the kinetic theory of the electrical double layer. Thus DD_0 in our treatment is identical with what has been simply called D heretofore. It is suggested that D_0 be called the diabattivity of free space, from διαβατός, passable.

The largest value of Γ_+ ordinarily observed is about 20 μ coul./cm.^{2} This is the value found on extreme cathodic polarization of a mercury surface in 0.3 M aqueous sodium chloride, for instance (figure 9). Under these conditions the cations will be expected to lie in a very compact layer, essentially a monolayer, although still formally a diffuse layer. The average spacing of the ions of the double layer will then be about 9.0 A. from center to center. This calculation includes an approximate correction for the ions normally present in that region from the solution and also takes into account the fact that there is a deficiency of anions amounting to about 3 μ coul./cm.^{2} in the double layer under these conditions. For comparison, the average spacing of ions in a 1.0 M solution of a z-z valent electrolyte is about 10.6 A., only a little greater than the figure named above. These considerations offer some justification for the assumption that the neglect of crowding effects does not invalidate the entire treatment. At the same time, they indicate that the results to be obtained cannot be accepted without some reservation.

The assumption is made through the use of equation 31 that the potential is a function only of x. This assumption has been questioned (88, p. 262) on the

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[21] If any one of the ionic types present in the solution at an appreciable concentration has a large solvation energy this statement is valid, for the development requires that equation 33 be valid for every ionic type in the solution.

grounds that the electric charge density at a given value of x is by no means constant on a microscopic scale. On the other hand, if the potential be defined by means of equation 33, as suggested, then since the work w_i has a definite value for each value of x, the value of the corresponding potentials will suffer from no uncertainty on this account.

It has become evident in recent years (e.g., reference 27) that the values of ψ encountered in the diffuse double layer are a good deal smaller than had commonly been supposed, and that the same is true of $d\psi/dx$, the field strength. It is the latter consideration which makes it reasonable to use the dielectric constant of the solvent in the calculations which follow, while the former avoids a difficulty associated with the use of equations 32 and 33. Thus at a potential of 0.3 volt, once considered easily attainable in unimolar solutions, equations 32 and 33 lead to the result that the concentration of the more abundant ion, assumed univalent, is about 10^5 times greater than in the interior of the solution. This is manifestly impossible in all but very dilute solutions, and if such potentials were actually possible in unimolar solutions, then the theory would necessarily be very greatly in error. It may appear that image forces are neglected in the following treatment. This is not so, since the effects of the "image" charges in the metallic surface are taken account of implicitly by giving a non-zero value to ψ at one boundary (see reference 72). Combination of equations 32 and 33 gives:

$$n_i = n_{0i}e^{-z_i\epsilon\psi/kT} \tag{34}$$

The charge density at any point is the sum of the charge densities of the individual ionic types, or

$$\rho = \Sigma\, n_i z_i \epsilon = \Sigma\, n_{0i} z_i\, \epsilon e^{-z_i\epsilon\psi/kT} \tag{35}$$

Substituting this in equation 31 gives the fundamental differential equation:

$$\frac{d^2\psi}{dx^2} = -\frac{4\pi\epsilon}{DD_0}\,\Sigma\, n_{0i} z_i e^{-z_i\epsilon\psi/kT} \tag{36}$$

This can be integrated once by introducing the identity

$$\frac{d^2\psi}{dx^2} = \frac{1}{2}\frac{d}{d\psi}\left(\frac{d\psi}{dx}\right)^2$$

which after substitution and integration gives:

$$\left(\frac{d\psi}{dx}\right)^2 = \frac{8\pi kT}{DD_0}\,\Sigma\, n_{0i}(e^{-z_i\epsilon\psi/kT} - 1) \tag{37}$$

The constant of integration has been evaluated by noting that in the interior of the solution $d\psi/dx = 0$ and $\psi = 0$.

For many purposes it is not necessary to integrate this equation further. According to Gauss' law (which may here be regarded as an integrated form of equation 31)

$$d\psi/dx = 4\pi\eta^d/DD_0 \tag{38}$$

where

$$\eta^d = \int_x^\infty \rho \, \mathrm{d}x \tag{39}$$

According to equation 39 η^d is the *surface* charge density, the total charge in a column of liquid of unit cross section extending from the plane in question (the one to which $\mathrm{d}\psi/\mathrm{d}x$ refers) on into the body of the solution where $\psi = 0$. Equation 38 is only valid when the dielectric constant is constant from $x = x$ to $x = \infty$. Since this assumption was already made in integrating equation 36, no new approximations are involved in the use of equation 38. The superscript *d* in η^d refers to the *diffuse* double layer.

Combining equations 37 and 38 gives η^d as a function of ψ.

$$\eta^d = \pm \sqrt{\frac{DD_0 kT}{2\pi} \Sigma n_{0i} (e^{-z_i \epsilon \psi/kT} - 1)} \tag{40}$$

Let

$$A = \frac{DD_0 kT n_{0i}}{2\pi}$$

For a *z-z* valent electrolyte equation 40 can be simplified to:

$$\eta^d = - A \sqrt{\exp (z\epsilon\psi/kT) + \exp (- z\epsilon\psi/kT) - 2} \tag{41}$$

$$= - A [\exp (z\epsilon\psi/2kT) - \exp (- z\epsilon\psi/2kT)] \tag{42}$$

$$= - 2A \sinh z\epsilon\psi/2kT \tag{43}$$

$$= - 11.72 \sqrt{c_i} \sinh 19.46\, z\psi \quad \mu \text{ coul./cm.}^2 \tag{44}$$

The negative sign is chosen because η^d is positive when ψ is negative and *vice versa*. Equation 44 is evaluated for aqueous solutions at 25°C. c_i is the concentration in moles per liter and ψ is in volts.

Up to this point in the treatment of the kinetic theory of the electrical double layer the equations refer to values of ψ anywhere within the diffuse double layer. If one substitutes for ψ in equation 44 the potential of the *outer Helmholtz plane*, designated by ψ°, one obtains the value of η^d for the *entire* diffuse double layer. From here on the symbol η^d will sometimes have this special meaning. It will be clear from the context which meaning is intended in any given case.

There are two kinds of capacity of the *diffuse* double layer to be considered, the differential capacity C^d and the integral capacity K^d. These are defined in terms of the potential of the *outer* Helmholtz plane, ψ°, as follows:

$$K^d = - \eta^d/\psi^\circ \text{ and } C^d = - \mathrm{d}\eta^d/\mathrm{d}\psi^\circ \tag{45}$$

$$K^d = \frac{2A}{\psi^\circ} \sinh z\epsilon\psi^\circ/2kT \tag{46}$$

$$C^d = \frac{z\epsilon A}{kT} \cosh z\epsilon\psi^\circ/2kT \tag{47}$$

$$= 228.5z\sqrt{c_i} \cosh 19.46\, z\psi^\circ \quad \mu\text{f/cm.}^2 \text{ at } 25°\text{C.} \tag{48}$$

At low values of ψ^o, the hyperbolic cosine is almost unity and both C^d and K^d (to which it is then equal) are constant, but this constancy does not extend to values of ψ^o comparable to those found in practice. Table 2 shows how K^d and C^d compare and also how they vary with ψ^o. Values in parentheses correspond to values of ψ^o beyond what can easily be achieved in practice. It will be noted that the maximum attainable value of ψ^o goes up with decreasing concentration, while the maximum value of C^d decreases slowly. Even in 10^{-3} M solution, however, this maximum value is very large ($\sim$ 300 μf/cm.^{2}), which means, according to equations to be developed later (52 and 53), that the capacity of the diffuse double layer exerts little influence on the observed over-all capacity at large positive or negative polarizing potentials. This fact is in some respects fortunate, since it is exactly under these conditions that the postulates of the theory are most unreliable. Even a very large error in the theory, percentagewise, will lead to only small errors in the expected properties of the double layer.

TABLE 2

Calculated differential and integral capacities, C^d and K^d, of the diffuse double layer for z-z valent electrolytes in aqueous solution at 25°C.

Capacities are in μf/cm.^{2}

CONCENTRATION		CHARGE × POTENTIAL OF OUTER HELMHOLTZ PLANE, $z\psi^o$						
		0.0 v	0.02 v	0.04 v	0.06 v	0.08 v	0.10 v	0.12 v
M								
1	K^d	228	235	252	285	(334)	(403)	(502)
	C^d	228	246	302	403	(568)	(820)	(1200)
0.1	K^d	72.2	74.3	79.9	90.0	105	128	159
	C^d	72.2	77.8	95.5	127	180	259	378
		0.12 v	0.14 v	0.16 v	0.18 v	0.20 v	0.22 v	0.24 v
0.01	K^d	50.2	63.9	82.9	109	(145)	(194)	(263)
	C^d	120	176	259	383	(565)	(835)	(1233)
0.001	K^d	15.9	20.2	26.2	34.4	45.8	61.5	83.2
	C^d	37.8	55.6	82.2	121	179	264	390

K^d and C^d are sometimes mistaken for the capacities of the whole double layer, which is quite erroneous because the potential ψ^o, to which the calculations refer, is very different from any potential one might think to use for a calculation of the over-all capacity. Moreover it is not true that $d\psi^o = dE$, which seems to be the assumption sometimes made.

The relation between the capacity of the whole double layer, in the absence of adsorbed ions, and the capacity of the *diffuse* double layer is found as follows: Let C^o and K^o be the differential and integral capacities of the region from the mercury surface to the outer Helmholtz plane. Then from electrostatic considerations alone (or as a definition of K^o)

$$-\eta^d = K^o(\psi^r - \psi^o) \qquad (49)$$

Remembering that K^o is not necessarily a constant, one writes also, as a definition of C^o:

$$- d\eta^d = C^o d(\psi^r - \psi^o) \qquad (50)$$

If ionic adsorption is assumed absent,[22] the charge on the diffuse double layer, η^d, is identical (except for sign) with the charge on the metallic surface, q, and ψ^r is identical with **E**. Therefore from equations 8 and 9:

$$- \eta^d = K\psi^r \text{ and } - d\eta^d = C\, d\psi^r \qquad (51)$$

Combining equations 45, 49, 50, and 51 one has

$$K = K^o K^d/(K^o + K^d) \qquad (52)$$

and

$$C = C^o C^d/(C^o + C^d) \qquad (53)$$

Therefore the integral capacity of the whole double layer is equal to the capacity of two condensers of capacities K^o and K^d connected in series; an analogous statement applies to the differential capacity.

The reasonableness of this result becomes apparent if one imagines two layers of charge placed at the outer Helmholtz plane, one equal to the charge on the mercury surface, the other of the same magnitude but of opposite sign. Such a system is readily seen to have a capacity given by equation 52 or 53.

For the theoretical evaluation of K and C, one needs to know K^o and C^o, which are not given by the theory and represent an as yet unsolved theoretical problem.

To judge from the appearance of the differential capacity curves (figure 5), fluorides show less ionic adsorption at ordinary potentials than any other salts.[23] This is presumed to be a consequence of the fact that the fluoride ion is hydrated (7) and that fluoride ion does not readily form covalent bonds with mercury. For the experimental evaluation of K^o and C^o, therefore, solutions of fluorides would seem to be particularly suitable. Concentrated solutions are more suitable than dilute, since K^d and C^d are then so large that their effect on K and C is minimized (equations 52 and 53). As a test of the theory so far developed the writer has calculated K^o and C^o from differential capacity data obtained with 1 M sodium fluoride, using the relations 52 and 53 together with equations 46 and 47 which had little effect. These values of K^o and C^o are shown in figure 11. It was assumed, then, that K^o and C^o depended only upon q (or η^d), and with the aid of this assumption and the equations named, the differential capacity C of more dilute solutions of sodium fluoride was calculated. The results are presented in figures 12, 13, and 14.[24]

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[22] Adsorbed ions populate the inner Helmholtz plane. Hence the absence of ionic adsorption insures that all of the ionic charge is accounted for in the diffuse double layer. Since cation adsorption is assumed negligible in any case, the values of Γ_+ already found and plotted in figures 9 and 10 represent the contribution of the cations to η^d. This quantity will later be designated as η^d_+. The sum of η^d_+ and η^d_- (plotted in the figures) then gives η^d.

[23] This fact will be subject to experimental verification when more accurate capacity data become available.

Although the agreement is not perfect, it is better than one would expect in view of the uncertain character of the theory of the diffuse double layer. Generally, the observed capacities on the cathodic side are lower than the calculated. The significance of this result cannot yet be stated with any assurance.

The minimum capacity at the electrocapillary maximum of dilute solutions arises from the greater average distance of the ions of the diffuse layer under these conditions. The maxima at small cathodic potentials[25] arise from the fact that C^o is decreasing while C^d is increasing. The calculations are not extended to large values of positive polarization, because it was felt that the assumed absence of ion adsorption would not then be justified. The conclusion which we draw from these results is that the theory of the diffuse double layer is accurate enough to be useful in spite of the dubious character of the assumptions upon which it is based.

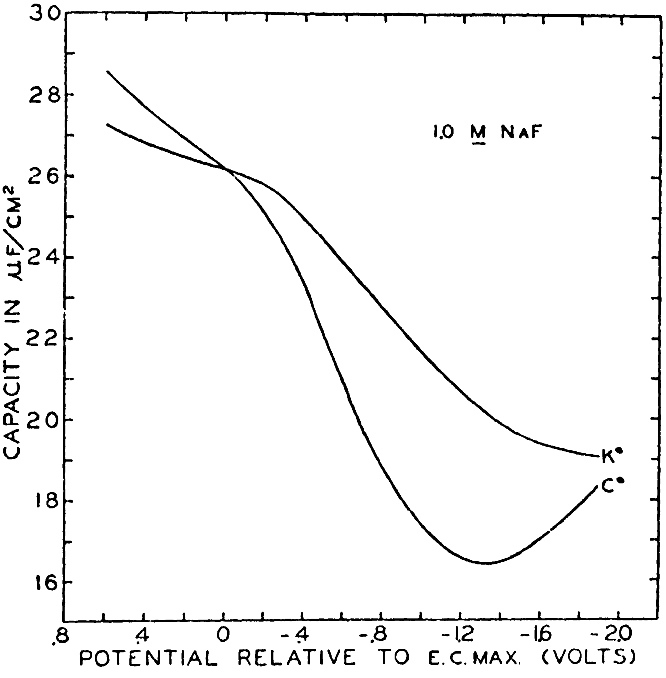

FIG. 11. Integral and differential capacities of the non-diffuse part of the double layer, calculated from data for 1 M aqueous sodium fluoride. This capacity is in series with the capacity of the diffuse double layer (table 2).

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[24] The values here given are of a preliminary nature, since the experimental data were not of the best.

[25] Vorsina and Frumkin (86) do not observe the effect except in the presence of polyvalent cations (see footnote 15).

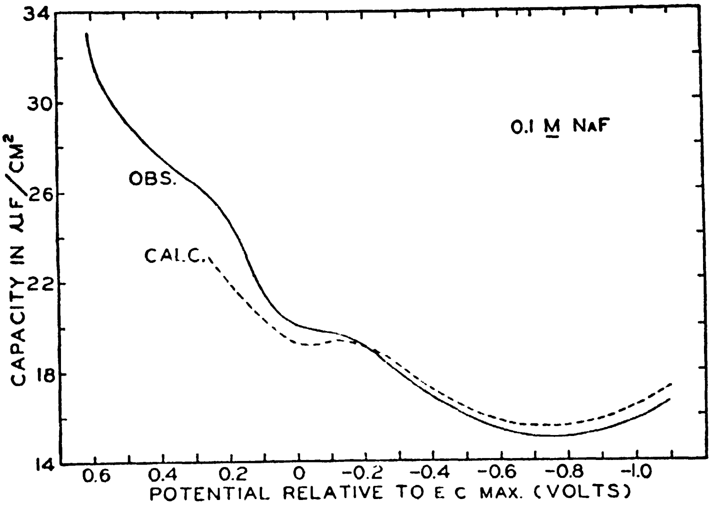

FIG. 12. Calculated and observed differential capacity of mercury in contact with 0.1 *M* sodium fluoride. *T* = 25°C. Experimental data obtained with 1.0 *M* sodium fluoride enter into the calculated values.

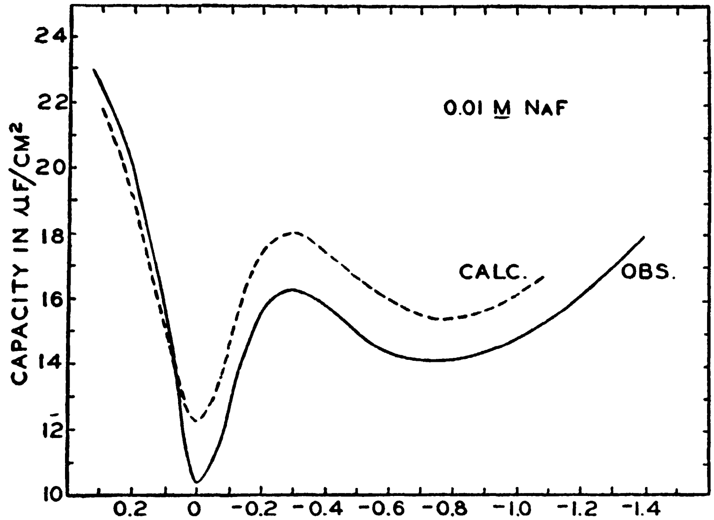

FIG. 13. Calculated and observed differential capacity of mercury in contact with 0.01 *M* sodium fluoride. *T* = 25°C. Experimental data obtained with 1.0 *M* sodium fluoride enter into these calculations.

The variation of K° and C° with E (figure 11) is probably due in part to the effect of crowding at the interface. Usually it is explained that anions, because of their greater polarizability, are more compressible, hence move closer to the interface, and therefore have a greater intrinsic capacity in a monolayer. Such an effect would cause the values of K° and C° to vary as anions replace cations in the double layer. But this explanation is hardly applicable to the fluoride ion, whose polarizability is about the same as that of a typical cation. Moreover, it ignores the fact that the polarizability of the cation plays no rôle. Thus potassium and sodium ions give almost the same values of C° and K°, in spite of having very different polarizabilities. It is probably true, however, that large polarizability of anions makes for high specific adsorption, which in turn produces large over-all capacity C. This effect presumably accounts for the large increase of capacity always observed on strong positive polarization.

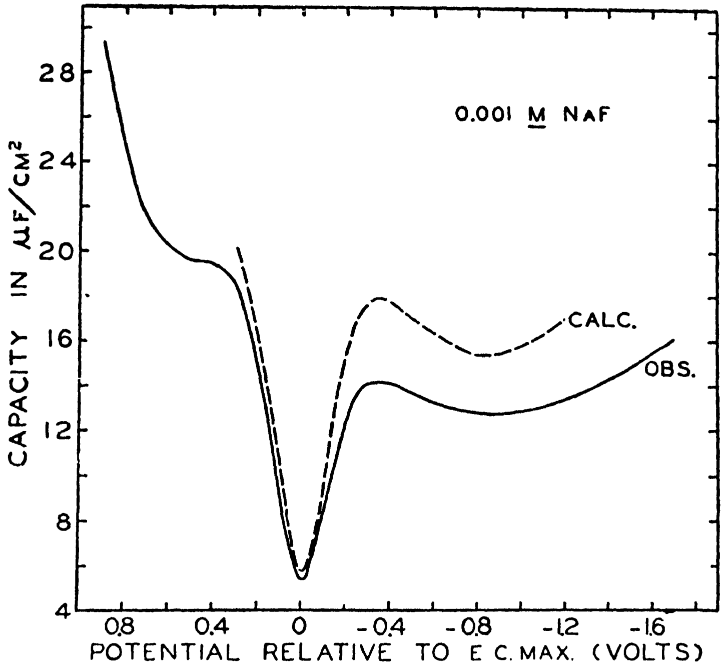

FIG. 14. Calculated and observed differential capacity of mercury in contact with 0.001 M sodium fluoride. $T = 25°C$. Experimental data obtained with 1.0 M sodium fluoride enter into these calculations.

Values of K° and C° depend very strikingly upon the anion present, even in the absence of specific adsorption. Thus the hydroxide ion, which is hydrated and not specifically adsorbed under negative polarization, differs greatly in its electrocapillary properties from the fluoride ion, which it would be expected to resemble. The investigation of problems such as this remains for the future.

It is now desired to find the manner in which ψ varies with x. Combining equations 43 and 38 gives:

$$dx = -\sqrt{\frac{DD_0}{32\pi kTn_{0i}}}\,\mathrm{csch}\,\frac{z\epsilon\psi}{2Kt}\,d\psi \qquad (54)$$

It should be recalled that this equation is restricted, through use of equation 43, to symmetrical valence types. It can be integrated through the identity

$$\int \operatorname{csch}\theta \, d\theta = \ln \tanh \left| \frac{\theta}{2} \right| + \text{const.} \tag{55}$$

whereupon

$$x - x_\infty = x' = -\sqrt{\frac{DD_0kT}{8\pi n_{0i}z^2}} \ln \tanh \left| \frac{z\epsilon\psi}{4kT} \right| \tag{56}$$

The constant of integration is x_∞. It is the value of x for which, if the differential equation were valid at all values of x, $\tanh z\epsilon\psi/4kT$ would become unity and ψ would become infinite. $x - x_\infty$ is therefore the distance of a point from this hypothetical plane of infinite potential, a distance designated by x'. Differences in x' are physically significant, although x' itself is not.

A new quantity, κ, is defined as

$$\kappa = \sqrt{\frac{8\pi z^2\epsilon^2 n_{0i}}{DD_0kT}} \tag{57}$$

$$= 3.28 \times 10^7 z\sqrt{c_i} \ \text{cm.}^{-1} \text{ at } 25°\text{C.}$$

and equation 56 takes the more compact form

$$x' = -\frac{1}{\kappa} \ln \tanh \left| \frac{z\epsilon\psi}{4kT} \right| \tag{58}$$

or

$$\psi = \pm \frac{4kT}{z\epsilon} \tanh^{-1} e^{-\kappa x'} \tag{59}$$

Equation 59 gives ψ as a function of x'. For small values of $e^{-\kappa x'}$ (large values of x'),

$$\tanh^{-1}\theta \sim \theta \qquad (\theta \ll 1) \tag{60}$$

and

$$\psi \sim \pm \frac{4kT}{z\epsilon} e^{-\kappa x'} \tag{61}$$

This result shows that at sufficiently large values of x', ψ is an exponential function of x' with a half-thickness of $\ln 2/\kappa$ or $2.11 \times 10^{-8}/z\sqrt{c_i}$ cm. at 25°C. For 1-1 electrolytes at unimolar concentration, the half-thickness is therefore of the order of magnitude of the ionic radius of the non-solvated ion. This small half-thickness points up the difficulty of defining potentials within the double layer. At lower ionic concentrations the half-thickness is greater, and the theory may be presumed to be more reliable.

The maximum value of the potential gradient may be calculated from equation 38. Numerical substitution shows that in aqueous solution at 25°C.

$$\frac{d\psi}{dx} = 0.1614 \times 10^6 \eta^d \ \text{volts/cm.} \tag{62}$$

where η^d is expressed in μ coul./cm.^{2}

η^d seldom exceeds 20 μ coul./cm.^{2}, a value which corresponds to about 3 × 10^6 volts/cm. This is not as large a field strength as previous calculations (of much greater complexity) had indicated (72). It is not certain whether or not the dielectric constant of water is greatly different from its usual value at this field strength. Malsch (69, 70, 71; see also 15 and 17, p. 358) finds the dielectric constant of water to be down 0.7 per cent at 250,000 volts/cm., the percentage change being proportional to the square of the field strength. By extrapolation, this would lead one to expect a very low dielectric constant at 3 × 10^6 volts/cm., but such a long extrapolation is obviously not to be given much weight. The whole argument is a little pointless in any case, since the practice of treating the electrical double layer as a continuum is presumably unsound for high values of η^d. One carries out the calculations primarily to obtain orders of magnitude and to investigate the reasonableness of the mathematical treatment.

The calculated maximum field strength is almost independent of the concentration and of ionic charge, because the maximum value of η^d is found to be almost independent of these.

It is often desirable to calculate the contribution to the charge of the diffuse layer made by the cations or anions individually. We define these quantities, termed η^d_+ and η^d_-, through the equations:

$$\eta^d_+ = \int_x^\infty (\rho_+ - n_{0i} z\epsilon)\, dx \tag{63}$$

$$\eta^d_- = \int_x^\infty (\rho_- + n_{0i} z\epsilon)\, dx \tag{64}$$

ρ_+ and ρ_- are the charge densities of cations and anions, respectively, both of which are assumed to have valences of absolute value z. The sum of η^d_+ and η^d_- is η^d.

$$\eta^d_+ + \eta^d_- = \int_x^\infty (\rho_+ + \rho_-)\, dx = \int_x^\infty \rho\, dx = \eta^d \tag{65}$$

Equation 35 gives for ρ_+

$$\rho_+ = n_{0i} z\epsilon e^{-\Psi} \tag{66}$$

where $\Psi = z\epsilon\psi/kT$. From equation 63

$$\eta^d_+ = n_{0i} z\epsilon \int (e^{-\Psi} - 1)\, dx \tag{67}$$

In this equation and in those which immediately follow, the limits of integration are from $x = x$ to $x = \infty$. Taking the square root of the square of the quantity in parentheses gives:

$$\eta^d_+ = n_{0i} z\epsilon \int \sqrt{e^{-2\Psi} - 2e^{-\Psi} + 1}\, dx \tag{68}$$

$$= n_{0i} z\epsilon \int \sqrt{(e^{\Psi} + e^{-\Psi} - 2)e^{-\Psi}}\, dx \tag{69}$$

Introducing equations 41 and 38 in succession gives:

$$\eta_+^d = z\epsilon \int \eta^d \sqrt{\frac{2\pi n_{0i}}{DD_0kT}}\, e^{-\Psi}\, \mathrm{d}x \tag{70}$$

$$= z\epsilon \int \sqrt{\frac{DD_0n_{0i}}{8\pi kT}}\, e^{-\Psi}\, \mathrm{d}\psi \tag{71}$$

This can be integrated to give:

$$\eta_+^d = A(e^{-\Psi/2} - 1) \tag{72}$$

Similarly one has that

$$\eta_-^d = -A(e^{\Psi/2} - 1) \tag{73}$$

The signs in equations 72 and 73 are chosen as they were for equation 41. By division one obtains the ratio of η_+^d to η_-^d, a ratio which depends only upon Ψ.

$$\eta_+^d/\eta_-^d = -(e^{-\Psi/2} - 1)/(e^{\Psi/2} - 1) \tag{74}$$

For low values of ψ, $\eta_+^d/\eta_-^d \sim -1$. For large values of $|\psi|$, η_+^d or $-\eta_-^d$ increased indefinitely, whereas the other quantity tends to the limit

$$\text{lim of } \eta_\pm^d = A \tag{75}$$

$$= 5.86\sqrt{c}, \quad \mu \text{ coul./cm.}^2 \text{ at } 25°\text{C}.$$

For a 0.3 M solution of z-z valent electrolyte, this gives as a limit of η_-^d the value 3.2 μ coul./cm.^{2} The observed limiting value of Γ_- in figure 9 is identical with this result, although the agreement is doubtless fortuitous. The largest observed value of Γ_- in unimolar sodium chloride is about 5.5 μ coul./cm.^{2}, which may be compared with 5.86 μ coul./cm.^{2} predicted by equation 75. This agreement lends some support to the kinetic theory of the diffuse double layer, although it is probable that these results make the theory look better than it really is.

Γ is composed of two parts representing the charge attributable to the adsorption of anions, η_-^i, and the charge attributable to repelled anions η_-^d. Then

$$z_-F\Gamma_- = \eta_-^i + \eta_-^d \tag{76}$$

η_-^i will always be negative or zero, and η_-^d will nearly always be positive or zero. Equation 72 can be used to evaluate Ψ for a given experimental value of η_+^d (taken to be identical with Γ_+). This value of Ψ can be used in equation 73 to evaluate the corresponding value of η_-^d. Since Γ_- is also known experimentally, one can evaluate η_-^i by equation 76. This procedure has been carried out for the evaluation of η_-^i represented in figures 9 and 10. There is relatively little uncertainty in this procedure, because η_-^d is small at potentials where η_-^i is appreciably different from zero.

Rice (81) has considered the nature of the diffuse double layer of electrons to be expected within the metallic phase itself. The treatment is similar to that here outlined for ions. By using a low value for the dielectric constant of mercury, Rice obtained values for the capacity of the diffuse double layer in mercury comparable to those observed for the whole double layer. It is more usual to regard the dielectric constant of an electronic conductor as sensibly infinite, however, in which case the calculated capacity of the diffuse double layer in the metallic phase is also sensibly infinite, and its capacity, being in series with the rest of the double layer, exerts no effect. This amounts to saying that in classical electrostatics no appreciable part of the potential drop occurs within the metallic phase itself. If it were otherwise, in fact, the nature and concentration of the electrolyte would not be expected to exert so decisive an influence on the properties of the double layer.

If one assumes (erroneously) that ψ^0 and ψ' are identical, it becomes possible to calculate $\Gamma^{\text{MAX}}_{\text{SALT}}$ (or η^d_+, which is the same thing at the electrocapillary maximum) from the theory of the diffuse double layer. The results of the calculation are in violent disagreement with experiment and also with any reasonable conception of the double layer. As an example, consider 0.1 *M* potassium iodide at the electrocapillary maximum. ψ', which is identical with ψ^r at the electrocapillary maximum, is observed to be -0.24 volt (table 1). If one assumes that this is also the value of ψ^0, then equation 72 gives for η^d_+ a value of 192 μ coul./cm.^{2} (an impossible result). This is to be compared with the experimental value of 9.1 μ coul./cm.^{2} At higher concentrations the disagreement is even worse and the calculated value even more impossible (4300 μ coul./cm.^{2} at 1 *M*). These results illustrate the necessity of distinguishing between ψ' and ψ^0, and also illustrate that ψ^0 must be the smaller of the two absolute magnitudes. It is these considerations which have led us to assume throughout the non-thermodynamic parts of this paper that the diffuse double layer does not extend to the inner Helmholtz plane and that low-molecular weight cations, which are not specifically adsorbed, do not populate that plane.

The dotted line in figure 8 gives the values of $\Gamma^{\text{MAX}}_{\text{SALT}}$ calculated in this manner for unimolar solutions. The disagreement reflects the fundamental nature of the error implicit in the assumption that $\psi^0 = \psi'$.

VII. THE THEORY OF THE COMPACT DOUBLE LAYER (8, 85, 87, 92)

In Section VI ionic adsorption has been assumed absent, meaning that no ions come closer to the interface than the outer Helmholtz plane. This assumption is probably satisfied to a good approximation on negative polarization of mercury in solutions of capillary-inactive electrolytes and even in solutions of capillary-active electrolytes when the active substance is an anion and when the polarization is great enough to repel these anions from the interface. Under most other conditions it is to be expected that an adsorption of ions occurs and that these adsorbed ions lie closer to the interface than unadsorbed ions. The layer of adsorbed ions is called the compact double layer or, better, the compact *part* of the double layer. The double layer is now a triple layer, but it is not generally so called.

Stern (85) worked out a theory of the compact part of the double layer based upon the Boltzmann distribution law. In spite of some defects, that theory still has much to recommend it. The central part of the theory will be here presented together with an indication of its limitations and the manner in which they may be removed.

Stern did not distinguish between what we have called the inner and outer Helmholtz layers, although he mentioned the possibility that such a distinction might be necessary. In the discussion which follows, this distinction will be made from the first.

Following Stern, let n^i be the number of adsorbed ions per square centimeter, n_{0i} the number of the same type of ion per cubic centimeter of solution, z^i the maximum number of ions that can be on 1 sq. cm. of surface, and z_{0i} the maximum number of ions for which there is space in 1 cc. of solution. If the course of a single ion is followed for some time, it will be found for a fraction of the time u^i at the interface and for a fraction of time u_{0i} in the solution. If no work were required to move an ion from the interior of the solution to a place at the inner Helmholtz plane, u^i/u_{0i} would be the ratio of the number of free places on the surface to those in the solution.

$$u^i/u_{0i} = (z^i - n^i)/(z_{0i} - n_{0i}) \tag{77}$$

If one considers not one ion but all the ions of a given type, it is evident that

$$u^i/u_{0i} = n^i/n_{0i} \tag{78}$$

If, finally, the amount of work w_i needed to move an ion from the interior of the solution to a free place at the interface is not zero, the right-hand term of equation 77 must be multiplied by the Boltzmann factor so that, with equation 78:

$$n^i/n_{0i} = (z^i - n^i)/(z_{0i} - n_{0i})e^{-w_i/kT} \tag{79}$$

Except in very concentrated solutions, n_{0i} is negligible relative to z_{0i}. With this simplification, equation 79 can be solved for n^i to give:

$$n^i = z^i \bigg/ \left(1 + \frac{z_{0i}}{n_{0i}} e^{w_i/kT}\right) \tag{80}$$

Stern identifies n_{0i}/z_{0i} with the mole fraction, which is admittedly only an approximation at best, and he also changes the number 1 in the numerator to 2. This latter change is made in order that n^i shall reach the limit $z^i/2$ when w_i has large negative values, it being assumed that nearly equal numbers of cations and anions will be adsorbed, in which case the monolayer cannot be more than half filled with ions of a given type. The logic here is not compelling, particularly if one distinguishes between the inner and outer Helmholtz planes, in which case ions of only a single type need populate the inner Helmholtz plane.

Experimentally it is found that the compact part of the double layer is not usually near to a complete monolayer. Thus a charge of 30 μ coul./cm.^{2} of chloride ions is about as large an adsorbed charge as one can conveniently deal with experimentally, and represents about 25 per cent of a complete monolayer.

Under these circumstances the unity in the denominator of equation 80 is small compared to $(z_{0i}/n_{0i})e^{w_i/kT}$, and one may write the equation in the form:

$$n^i = \frac{z^i}{z_{0i}} n_{0i} e^{-w_i/kT} \tag{81}$$

$$= 2rn_{0i}e^{-w_i/kT} \tag{82}$$

In equation 82, r is the radius of the non-solvated ion. The quantity z^i/z_{0i} has been set equal to $2r$, because the thickness of the region in question is to the thickness of a centimeter cube as $2r$ is to 1.

Equation 82 could have been derived directly by a consideration of the ratio of the probability that an ion would be in the solution to the probability that it would be in the interface. The numerical coefficient in equation 82 would then be 1 or 2, depending upon whether the mean free path of the ions is large or small compared to r. If the mean free path is short, spatial considerations are all that matter and the coefficient is 2; if the mean free path is long, the fact that ions can enter from only one side reduces the number of ions at the interface by one-half.

The work w_i may be divided up formally into a chemical and an electrostatic work term:

$$w_i = z_- \epsilon(\psi^i - \phi^i_-) \tag{83}$$

In this equation ψ^i is the electrical potential of the inner Helmholtz plane as before, and ϕ^i_- is an adsorption potential of the anions. It is only under special circumstances that this division has any physical significance, as explained below. Equation 83 differs slightly in form from Stern's equation because we find it more convenient to express ϕ^i_- in units of electrical potential, but the physical meaning is the same. Stern considered the possibility that both positive and negative ions might be adsorbed simultaneously, but since this case is experimentally rare and theoretically very complicated, we prefer to assume that only one type of ion is adsorbed. For cation adsorption equation 83 would be replaced by

$$w_i = z_+ \epsilon(\psi^i + \phi^i_+) \tag{83'}$$

There is no general experimentally unambiguous procedure for dividing up w_i in this manner. The potential of the inner Helmholtz plane, ψ^i, may be calculated from equation 28 if one assumes that K^i is a constant. Although K^i does appear to be nearly constant under the conditions for which it can be evaluated (the Γ_+^{MIN}-potential), it is only on this assumption that ψ^i can be evaluated in general. At the electrocapillary maximum, however, ψ^i is known regardless of K^i (it is equal to ψ^r), and one can say in that case at least that ϕ^i is defined unambiguously by equation 83 or 83′. The equations given in this section, together with equations 43 and 28 and the identity

$$\eta = -q = \eta^i + \eta^d \tag{84}$$

constitute the essential parts of the Stern theory.

There are not sufficient equations in the Stern theory as here outlined to permit the calculation of the properties of the double layer without recourse to experimental data. The most significant use of the theory which can be made at present is the calculation of ϕ^i_- from equations 82 and 83 taken together with experimental data like that shown in figure 9. Values of ϕ^i_- obtained in this way are plotted in figure 15. The principal result of this calculation is the fact that ϕ^i_- varies with q. As the mercury becomes more positive, the chemical binding energy becomes greater. As already explained, this result is attributable to the increased stability of the electron-pair in a covalent bond in the presence of a positive charge.

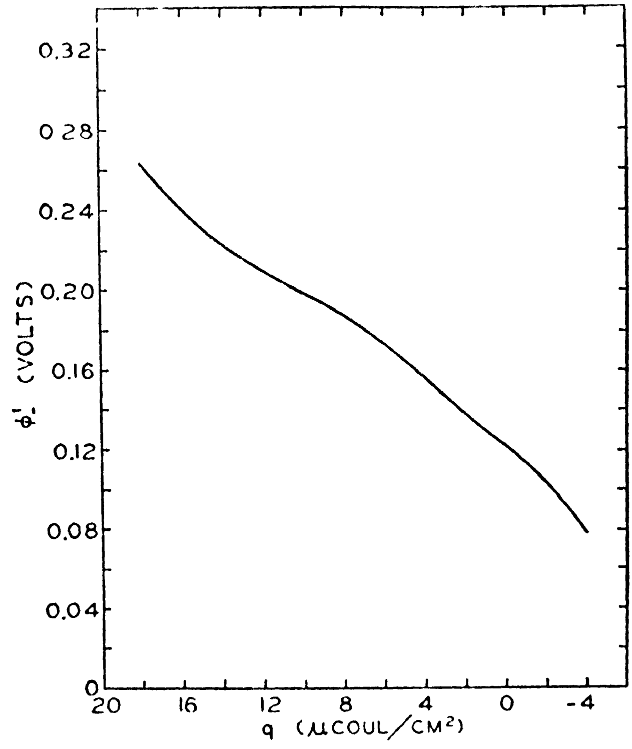

FIG. 15. Specific absorption potential, ϕ^i_-, for chloride ion on mercury as a function of q, the electronic charge on the metallic surface. Computed from data presented in figure 9.

In the original Stern theory it was implied that in the absence of ionic adsorption, ϕ^i_+ and ϕ^i_- were zero. This is not quite right in terms of our present concepts, for the work required to move an ion from the interior of the solution to a place on the interface would not then be zero but would be positive, owing to the work needed to displace the solvent sheath on the side of the interface. As a result of this, ϕ^i_- is positive and η^i would be nearly zero when ψ^i is zero, a result which differs from the prediction of the original Stern theory but which agrees with the physical picture we have here adopted, i.e., the inner Helmholtz layer should not be populated appreciably in the absence of specific adsorption.

Although equation 82 was derived upon the assumption that the monolayer of adsorbed ions was far from complete, it is possible to interpret w_i in such a manner that the equation retains its validity at all ion densities. If w_i is regarded not merely as the energy needed to move the ion into a previously vacant space but as the energy needed to make a vacancy and to move the ion into it, it will be evident that n^i cannot exceed a monolayer even according to equation 82. In this sense equation 82 is no less reliable than equation 80.

Equation 82 may be combined with equation 83 and rewritten in terms of charge to make it more suitable for calculation.

$$\eta^i = 2z_-\epsilon r n_{0i} \exp \{-z_-\epsilon(\psi^i - \phi^i_-)/kT\} \tag{85}$$

$$= 3.86c_i z_- \exp \{-38.92z_-(\psi^i - \phi^i_-)\} \; \mu\text{coul./cm.}^2 \text{ at } 25°\text{C. if } r = 2\text{ A.} \tag{86}$$

In these equations, as in those of preceding sections, z_- is the valence number, including sign, of the anion which is adsorbed. Cation adsorption is assumed absent.

We conclude this section with figures designed to illustrate the structure of the electrical double layer.

Figure 16 shows the potentials within the double layer calculated from equations 28, 43, 59, and 72, together with the experimental data represented in figure 9. A distance of 3 A. from the interface has been assumed in plotting the potential of the outer Helmholtz plane, but this number does not enter into the calculations. It is only an accident that the Γ_+^{MIN}-potential coincides with the potential of the electrocapillary maximum in this case. Perhaps the most significant feature of figure 16 is the fact that the potential of the inner Helmholtz plane reaches a maximum, a result which might have been anticipated from the fact that Γ_+ reaches a minimum.

Figures 17–19 show schematic representations of the electrical double layer under various conditions of polarization. Large circles represent an excess of an ion type assumed to be solvated. Dotted circles represent a deficiency of an ion type. Small circles represent an excess of a non-solvated ion; minus or plus signs not surrounded by circles represent electrons or a deficiency of electrons. The manner in which the potential varies with distance is indicated in the box in each figure. The magnitude of ψ^0 is exaggerated in order to bring out the character of the variation of ψ with x in the diffuse double layer.

VIII. POTENTIAL DIFFERENCES BETWEEN DISSIMILAR PHASES (3, 47, 48, 49)

Progress in the study of the electrical double layer calls for a very clear understanding of the term "electrical potential difference" as applied to dissimilar media. In the discussion here given the author has refrained from introducing any new concepts. There is not much room for real disagreement in this subject nowadays, except in regard to terminology and conventions. It is hoped that the treatment here given will make it possible for future authors to discuss the subject accurately without prolonged explanations.

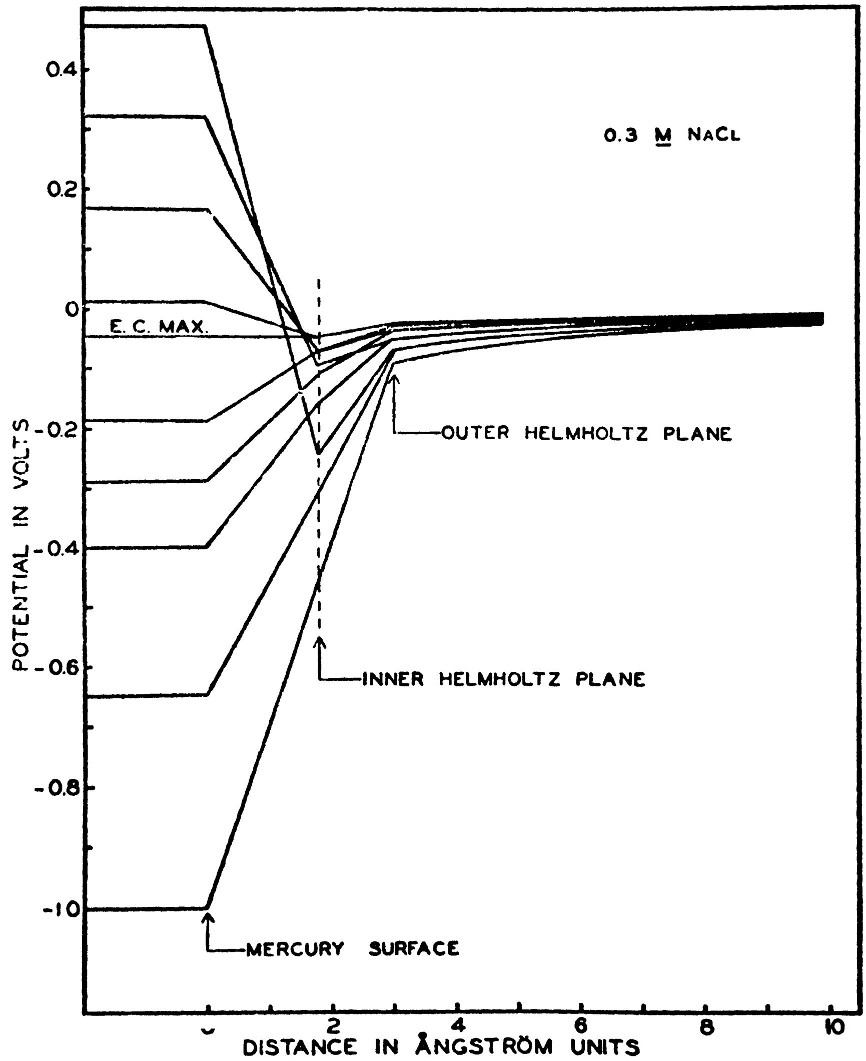

FIG. 16. Potentials in the electrical double layer between mercury and aqueous 0.3 *M* sodium chloride solutions at 25°C. at various polarizing potentials. Values calculated from data in figure 9. The potentials are "rational" in the sense defined in the text. Note that the potential of the inner Helmholtz plane reaches a maximum as the polarizing potential is varied from one extreme to the other.

Guggenheim in 1929 wrote a classic paper (47) in which it was demonstrated that absolute or "true" potential differences between dissimilar phases are unmeasurable because they are not defined. Moreover, it was pointed out that attempts to define an absolute potential difference are unnecessary, since it is possible to describe all actual experimental observations in terms of potential differences of the types already known. In a subsequent paper (48) Guggenheim allowed that it was possible to define new types of potential difference which might prove to be convenient for some purposes, but the important point remained that there was no necessity for doing so.

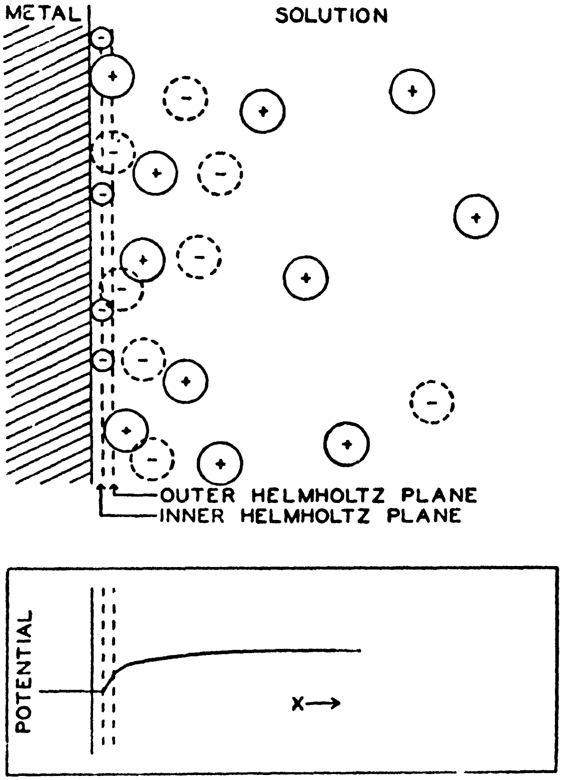

Fig. 17. Schematic representation of the electrical double layer at the potential of the electrocapillary maximum. Small circles represent adsorbed ions. Large circles represent solvated ions. Dotted circles represent "ghosts", ions which would be present if the double layer were not there.

In a third, seemingly little-known paper (49), Guggenheim suggested a definition of the activity coefficient of individual ionic species. The definition also serves to define the potential difference between dissimilar salt solutions in contact, or between two concentrations of the same salt solution. There was no contention that the suggested definition gave values of an "absolute" potential difference except with infinitely dilute solutions, where the quantity was defined anyway. The only advantage claimed was one of convenience and, all important, the advantage of not conflicting in any way with established thermodynamic usage. The basis of the definition was an assumption that the ratio of the individual ionic activity coefficients in a salt solution is given by the Debye–Hückel limiting law. This much can be assumed without thermodynamic contradiction. Its chief virtue is that it makes it possible to talk about individual ionic activities and liquid-junction potentials without ambiguity. There is also a certain advantage in that it makes it possible to calculate liquid-junction potentials with less confusion of thought than had been the case formerly. If the idea is firmly grasped that the potential differences in question are not "absolute", there can be a great gain in clarity of exposition and of thought in Guggenheim's proposal.

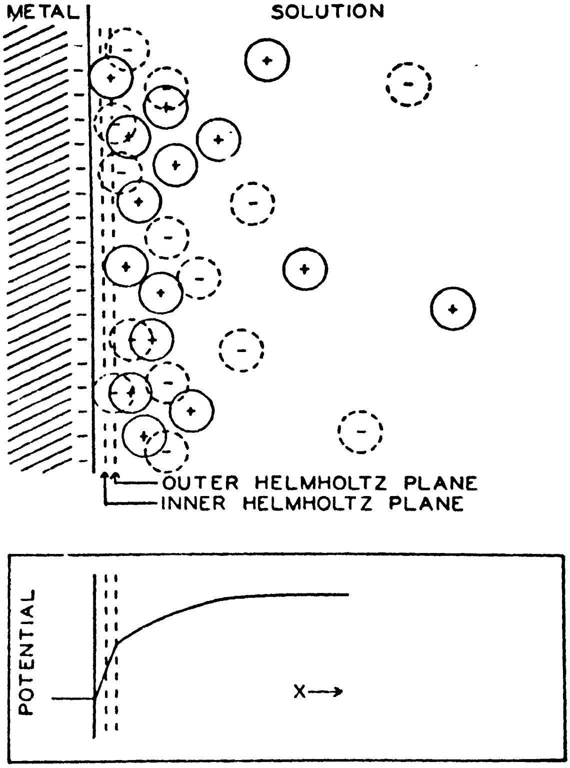

FIG. 18. Schematic representation of the electrical double layer with negative polarization. Note absence of adsorbed ions and increased concentration of positive ions as compared with figure 17. The concentration of "ghosts" is also increased.

Where liquid-junction potentials have been mentioned or used in the preceding parts of this review, Guggenheim's definition has been assumed.

The potential difference between immiscible phases is not defined by Guggenheim's assumption. Again it is convenient to have a working definition, provided one can keep clear of any suspicion of having proposed a definition of absolute potential difference. The rational potential difference, ψ^r, defined in Section III, is an example of a useful working definition.

The potential difference between two dissimilar isotropic metals in contact has been frequently misunderstood. There are two kinds of potential difference between dissimilar metals in contact which are measurable, the Volta or contact potential difference and what may be called the electron potential difference. The former can be measured only with very clean surfaces; it is the work required to move unit electric charge from the interior of a macroscopic cavity in one metal to the interior of a macroscopic cavity in the other. The walls of the cavities are assumed to be clean, in which case the work involved is a definite quantity which can be measured in a variety of ways (4). It is, for instance, the difference

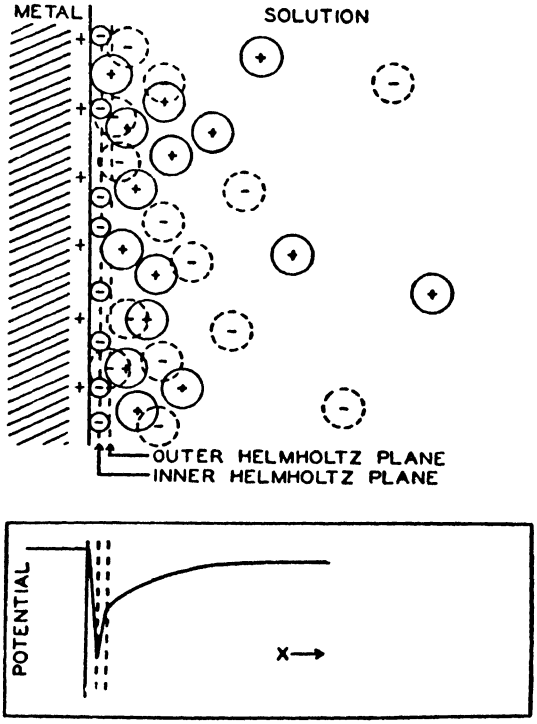

Fig. 19. Schematic representation of the electrical double layer with positive polarization. Note presence of adsorbed anions. Diffuse double layer is identical with that depicted in figure 18.

in the work functions of the metals, or minus the potential difference which must be put in series with the wire connecting the two metals in order to permit their clean surfaces to be moved toward or away from one another without a flow of electric current through the connecting wire. A constant temperature throughout the system is assumed.

The Volta potential difference between metals in contact is not affected by contamination of the metals at the point of junction, because any number of electronic conductors can be inserted between two metals without altering the electronic equilibrium of the metals. Thus as long as the contact is electronic (not ionic), the Volta potential difference does not depend upon the cleanliness of the junction. The surfaces at which the *measurement* is made, however, must be clean.

The Volta potential difference is similar in magnitude to the E.M.F. established when the two metals are made the electrodes in a galvanic cell containing solutions of their salts. This is because the electron affinity of the uncharged metal atoms is a major controlling factor in both. Zinc has a lower electron affinity than copper; hence zinc in contact with copper loses electrons until it becomes positively charged, the copper becoming negatively charged. Because of its lesser electron affinity, zinc lies higher in the electromotive series than copper,[26] and its behavior in galvanic cells therefore depends upon one of the same factors as does its Volta potential.

It was supposed at one time that the similarity of Volta potentials and electrode potentials indicated the presence of a film of moisture between metals in contact. Today such a supposition appears unthinkable on any grounds, not the least of which is that the sign of the potential difference is wrong.

The *electron* potential difference between two metals will be defined as the work required to transfer an electron (not an idealized charge) from one phase to the other. If the metals concerned are in contact and at uniform temperature, this work will evidently be zero.[27] The electron potential difference is what is measured by all voltmeters, potentiometers, and the like, including electrometers.

If the ends of a uniform bar of metal are maintained at different temperatures, the electron potential at the two ends is not the same, as is evidenced by the existence of the thermoelectric effect. It is customary to explain this effect as arising from differences in the contact potentials at the two junction temperatures, but this explanation is misleading since it ignores the facts (*a*) that contact (i.e., cavity) potential differences must also be presumed to exist between two parts of a uniform bar of metal at different temperatures and (*b*) that what is measured is not a contact potential but an electron potential difference. Although it is undoubtedly true that contact potentials do depend upon temperature, the connection between this fact and the thermoelectric effect is remote. It is much more satisfactory to explain it as the difference in the electron potential differences generated by dissimilar metals maintained at the same terminal temperatures.

Since contact (Volta) potentials are a measure of the work required to move a unit charge from a point in the vicinity of one surface to a point in the vicinity of another, it is to be expected that all methods of measuring Volta potentials should be extremely sensitive to changes in the cleanliness or character of the surfaces in question, as is found to be the case. This fact is sometimes useful in deciding what kind of potential a given experiment measures. As mentioned above, however, the contact potential of electronic conductors does not of itself depend upon the cleanliness of the surface. It is only in the *measurement* of contact potentials that surface cleanliness becomes important.

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[26] The position of a metal in the electromotive series also depends upon the hydration energy of the ion formed, but this effect is not dominant.

[27] This statement assumed no continuous current flow from one phase to the other.

The potential of the electrocapillary maximum, $-\mathcal{E}^{\text{MAX}}$, observed with dilute amalgams or with metals other than mercury leads to interesting results. Thus an amalgam containing 0.004 per cent of cadmium gives with normal potassium chloride a value of 0.625 volt (12) instead of the 0.56 volt observed with pure mercury. Somewhat similar results are obtained with thallium amalgams in sodium sulfate solutions (30), and it is noteworthy that metallic gallium gives a value of about 0.9 volt in potassium chloride solutions (29). These variations can be accounted for in part by specific adsorption of anions and in part, perhaps, by reorientation of solvent molecules, but it is also true that the contact potential which arises when the mercury in the reference electrode is joined to the other metal composing the polarized electrode shifts the potential of the electrocapillary maximum by an equal amount (26).

There is a long-standing argument concerning the question of where the potential difference of a galvanic cell arises. The question can be answered correctly once it is accurately stated. To the question—Where does the electron potential difference arise?—there can be but one answer. It arises wholly within the cell. Since the electron potential of the solution is undefined, one cannot be more explicit. If one asks instead—Where does the cavity potential difference (the electrostatic potential difference) arise?—the answer is likewise unambiguous. It arises partly at the electrodes and partly at the junction between the metals which compose the electrodes. Since electromotive force is a form of electron potential difference, no part of the E.M.F. of a cell can be said to arise from the contact potential of the metallic electrodes.

Cavity potential differences between mercury and potassium chloride solutions have been measured by Klein and Lange (57), the junction between the two phases being made by means of a calomel electrode. In this way it was hoped to measure a "true" potential difference of the calomel electrode, but it is now evident that what was measured was only a little different from the potential of the electrocapillary maximum. The effects of the specific adsorption of anions on mercury were surely eliminated, but not the effects of different ionic hydration energies, which build up what are known as surface potentials (*vide infra*). Moreover, and even more serious, the method does not eliminate the effects of water orientation on the mercury, for water vapor was of necessity in contact with the mercury. Even if all of these effects could have been eliminated, no "true" potential difference would have been measured, since one knows nothing about the potential gradients which may exist at a clean surface of mercury. This all amounts to saying again that "true" potential differences cannot be measured because they are not defined.

The "true" potential difference between a metal and a solution has sometimes been defined as the work required to move an ion of the metal from the interior of the metal to the interior of the solution. It is not reasonable to call this the "true" potential difference, for at the very least one would have to correct for the hydration energy of the ion in solution and the "solvent" effect of the metal on the metallic ion. A metal in equilibrium with a solution of one of its salts reaches a state such that no work is needed to move the ion of the metal from one phase to the other. But no one would suggest that the true potential difference in all such cases is zero.

Cavity potential differences have been measured for dissimilar solutions joined by salt bridges (24, 32). These measurements yield "surface potentials", a good approximation of the work required to move a test ion out through one interface and back through another. The second solution is so dilute that ionic accumulation at its interface may be ignored, and since the solvent effects on the test ion presumably cancel, what one has is an approximate measure of the work done in moving an idealized electric charge through any potential gradients set up by the presence of ions in the air–solution double layer of the more concentrated solution. It is found that the hydration energies of the ions are the controlling factor. Those ions (generally anions) which are least readily hydrated seek positions in the surface, making the surface negative to the interior of the solution. The order of the effectiveness of the anions in this regard is similar to that of the Hofmeister series, being $CNS^- > ClO_4^- > I^- > NO_3^- > Br^- > Cl^- > OH^- > F^-$ (32).

Much larger surface potentials are observed with surface layers of neutral but polar molecules (1, p. 133). These layers of molecules also occur at the electrical double layer between mercury and salt solutions containing small amounts of sparingly soluble organic substances (31, 34, 35, 37, 38). Although these layers are most often monolayers, the experimental evidence of Gorodetskaya and Frumkin (31, 35) indicates that polymolecular layers may form when the surface layers are compressed. If the potential of the mercury is made strongly positive or strongly negative, the attraction of the surface for ions exceeds its attraction for the polar molecules, and the latter are displaced. This displacement phenomenon sometimes occurs over a small range of potentials and gives rise to sudden changes in the charge of the double layer. This leads to large values of the differential capacity and more or less abrupt changes of slope of the electrocapillary curves. This behavior is exhibited by solutions of heptyl alcohol in an inert electrolyte, for instance, as is shown by figures 20 and 21. The capacity is almost uninfluenced by the frequency of the current used in the measurement, but the apparent electrical resistance of the adsorbed layer increases with decreasing frequency. This phenomenon has been studied and explained by the author as arising from the fact that the true resistance of the adsorbed layer is not the directly measured resistance minus the resistance of the solution because the resistance of the solution is in series with the capacity of the double layer, whereas the resistance of the adsorbed layer is in parallel with its capacity (43).

IX. TIME LAG AND POLARIZATION RESISTANCE AT AN IDEAL POLARIZED ELECTRODE

It is frequently observed that the establishment of complete equilibrium at an interface may be a slow process requiring times of the order of seconds or more. Thus it is well known that the surface tension of some types of solutions changes with time after the formation of a fresh surface (5, 18). The E.M.F. of galvanic cells frequently reaches equilibrium only slowly, and the attainment of stable electrokinetic potentials may be a matter of days (95). In the two latter cases a slow step can be postulated which does not demand that the actual orientation of ions in the double layer be slow. Thus the slow approach to a state of equilibrium in a calomel cell is undoubtedly to be attributed to the fact that a solid substance, mercurous chloride, is involved in the reaction by which equilibrium is attained:

$$Hg_2Cl_2 + 2e^- \rightarrow 2Hg + 2Cl^-$$

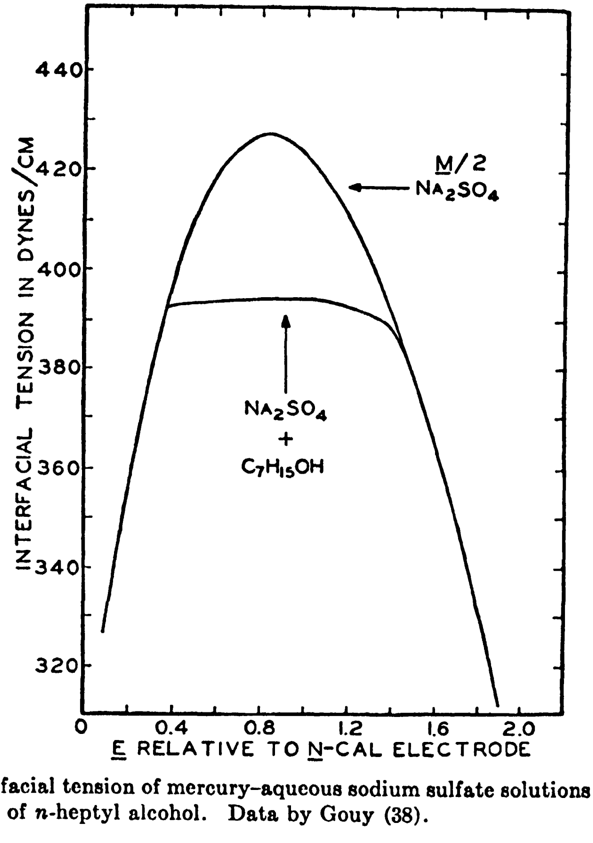

FIG. 20. Interfacial tension of mercury-aqueous sodium sulfate solutions with and without the addition of *n*-heptyl alcohol. Data by Gouy (38).

This reaction can proceed only when a mercurous chloride molecule is lying next to the mercury surface with the mercury ion favorably situated to receive the charge. This reaction does not necessarily take place instantaneously and in the amounts required by Faraday's law when a small current is passed through a calomel cell, since the capacity of the double layer is sufficient to supply a large charge with only a small change of potential. The above reaction then slowly restores the system to its equilibrium potential.

The slow attainment of equilibrium in the setting up of certain electrokinetic potentials is most probably associated with a slow change in the character of the surface (95). The slow change of surface tension exhibited by certain types of solutions is not yet satisfactorily explained, but is probably not attributable to a time lag in the formation of the double layer, once the necessary particles arrive at the surface.

An upper limit may be set to the time required to establish *ionic* equilibrium in the double layer at a mercury surface. According to measurements made by the author (43), a 1 sq. cm. mercury surface in a solution of 1 *M* sodium chloride exhibits an apparent resistance, commonly termed a polarization resistance, not in excess of 0.02 ohm and possibly considerably less. The capacity of the interface under the conditions of this experiment was about 18 μf/cm.^{2} The polarization resistance is in series with the capacity. The time constant of such a combination is RC or 3.6×10^{-7} sec. Thus the time required for virtually complete establishment of ionic equilibrium within the double layer is a microsecond or less. In practice the attainment of equilibrium will be delayed by the

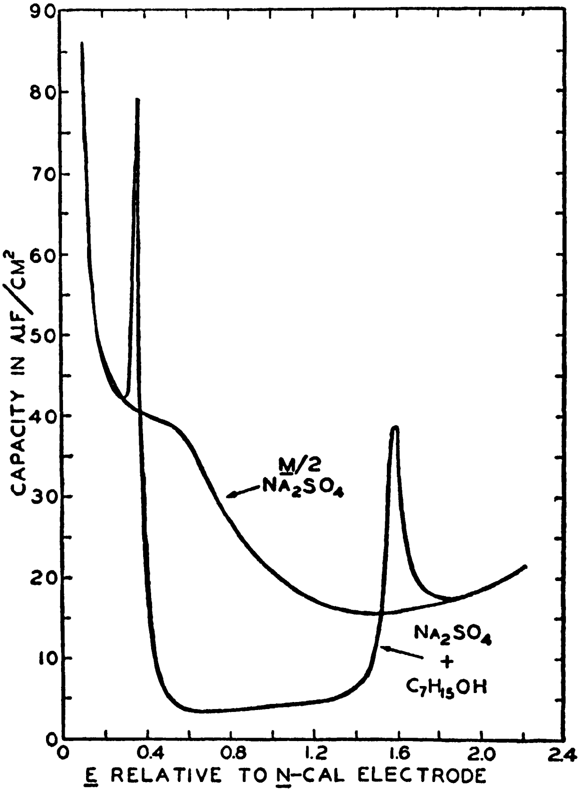

FIG. 21. Differential capacity of double layer between mercury and aqueous sodium sulfate solution with and without the addition of *n*-heptyl alcohol. The peaks do not occur exactly at the potentials of the breaks in the electrocapillary curve (figure 20), presumably because the temperature (and therefore the solubility of heptyl alcohol) was different in the two experiments.

finite resistance of the solution, of course, but that is a separate matter. The time constant of such delay is again given by RC, where R is now the total resistance between the electrodes and C is the series capacity of the electrodes.

The polarization resistance exhibited by other types of electrodes is associated with the occurrence of chemical reactions at the electrodes (43, 56, 90, 91). These reactions cause changes of concentration of the reactants at the interface, and because of the diffusion of these reactants or because the reactions are not rapidly reversible, the back E.M.F. does not remain in quadrature with the imposed alternating potential (82). A back E.M.F. not in quadrature with the imposed E.M.F. manifests itself as an electrical resistance in series (or in parallel) with the electrode. It has been shown both practically and theoretically (43, 44) that the changes of concentration which occur at an ideal polarized electrode give rise to diffusion effects too small to result in measurable polarization resistance. The electrical double layer therefore behaves very nearly like a pure capacitance.

X. CONCLUSION

A complete discussion of the applications of the theory of the electrical double layer would involve a discussion of electrokinetic phenomena, of the stability of colloids, of the conductance and chemical potentials of electrolytic solutions, of the behavior of clays and carbon black in suspension, of membrane equilibria, of hydrogen overvoltage, of the theory of corrosion phenomena, and of other phenomena not usually thought of as related to the double layer. Since the author has not had first-hand experience with most of these subjects, and since in any case excellent reviews of most of them are already available, they are omitted from this review. There are a few points upon which additional comments by the author may not be out of place, however.

At the surface of a non-metallic particle in a salt solution there exists an electrical double layer no different in principle from those which we have discussed above. It is convenient to regard the *neutral* surface of the particle as the counterpart of the metallic surface. Adsorbed ions then produce a charge on the particle, but since this is not an electronic charge, the particle is analogous to the metallic surface *at its electrocapillary maximum*. Beyond this layer of adsorbed ions lies the diffuse double layer, whose maximum potential ψ^0 is presumably to be regarded as the ζ-potential. At the isoelectric point this ζ-potential is zero, corresponding to a state in which the concentrations of the ions in the solution are so adjusted that positive and negative ions are equally adsorbed or unadsorbed (see Verwey (86a)).

Many attempts have been made to elucidate the structure of the double layer from studies of hydrogen overvoltage phenomena. In the opinion of the author, these phenomena are complicated by factors not yet well understood, with the result that reliable information about the double layer is not obtained in this way. There can be little doubt, however, that the high overvoltage of hydrogen on mercury is occasioned by the large activation energy associated with the reaction

$$H_3O^+ + e^- \rightarrow H + H_2O$$

since this reaction is highly endoenergetic (65). The fact that mercury is a poor catalyst for the *gas* reaction

$$H + H \rightarrow H_2$$

indicates that hydrogen atoms are not strongly bound to mercury, but does not indicate that this latter reaction is slow when the necessary third body (which may be mercury) is present, as it is during the reduction of hydronium ions. A critical discussion of the theories and experimental data pertaining to hydrogen overvoltage on mercury is given by Frumkin (28).

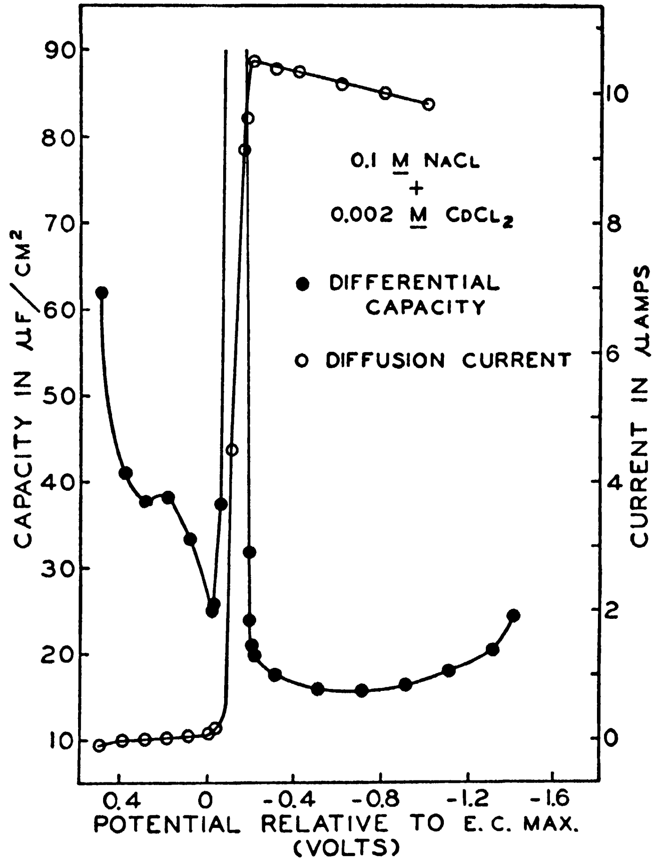

FIG. 22. Differential capacity observed in the presence of traces of reversibly reducible substance (Cd^{++}). Open circles show polarographic diffusion current for same solution.

When the reduction of an ion can occur reversibly, the apparent capacity of an electrode is enormously increased (42). An example of this effect is given in figure 22. The capacity is increased in this manner because the reduced form of the ion acts as a reservoir of charge. The concentration of the reduced form of the ion is fixed either by the potential or by the rate of diffusion of the ions to the surface, depending upon whether one is below or above the "half-wave potential." When the potential of the metallic electrode is made so strongly negative that the concentration of the reduced form of the ion is limited by diffusion, changes of potential cause no further change in the concentration of the reduced form of the ion, and the differential capacity becomes normal. This is a particularly good illustration of an electrode which is not ideally polarized acting like one which is.

The enhanced capacity caused by the reversible reduction of ions has been called by the author (42) a "pseudo-capacity," since it does not correspond to any bound charge except in the senso that neutral metallic atoms represent bound charge. This pseudo-capacity is observed on extreme cathodic polarization of sodium, potassium, rubidium, ammonium, and tetramethylammonium salts and presumably would be found with practically all cations. Hydronium ions do not give this effect, however, which can only mean that hydronium ions are not reduced reversibly at a mercury cathode, a result in harmony with the supposition that the reduction of hydronium ions on mercury is a process requiring activation energy. This must be regarded as strong support for the slow-discharge theory of hydrogen overvoltage mentioned above.

The reduction of oxygen on mercury does not give rise to any pseudo-capacity (42). This observation indicates that the first step in the reduction of oxygen

$$O_2 + 2H_2O + 2e^- \rightarrow H_2O_2 + 2OH^-$$

is a slow step, a fact which was known independently from the fact that it exhibits overvoltage. The absence of pseudo-capacity from the reduction of oxygen is fortunate for the making of differential capacity measurements, since the last traces of oxygen are difficult to remove from aqueous solutions at room temperature.

The reduction of nitrate ion is irreversible by the criterion of the absence of pseudo-capacity, a result which will occasion no surprise.

As an analytical tool the measurement of the pseudo-capacity at a dropping-mercury electrode might be found to possess the advantage of high sensitivity in the presence of small amounts of substances which are reducible but not reversibly reducible. The technique would be a modified form of polarography, but its greater complication would limit its usefulness to cases where ordinary polarographic methods fail. As a tool for investigating chemical reactions at an electrode, however, it can hardly be excelled.

References mentioned in the text and listed below are not comprehensive but include only those best suited to illustrate the points under discussion. In nearly every case the references cited give all of the essential information and provide a key to the earlier literature. Two other recent and fairly extensive reviews of electrocapillarity are those of Butler (10) and of Adam (3), to which the reader is referred for information about topics not here discussed.

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THE EFFECTS PRODUCED BY DIFFUSION IN AQUEOUS SYSTEMS CONTAINING MEMBRANES

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I. INTRODUCTION

The movement of molecules and ions through membranes is of fundamental biological importance, inasmuch as the entire content of all living cells has entered these cells through membranes permeable only to molecules and ions. In spite of the importance of this movement, the mechanism by which cells obtain a vital fraction of their contents at the expense of osmotic work is still unknown. Simple diffusion accounts for a large part of the movements of substances in and out of living systems but is of itself insufficient to account for all the observed facts. It is the purpose of this review to point out the various effects that can be produced by diffusion through membranes, so that effects that cannot be explained by simple diffusion will be more clearly apparent.

There have been an almost embarrassing number of reviews of various aspects of diffusion and permeability. In fact, it would hardly be an exaggeration to say that there are more reviews of diffusion than accurate measurements of diffusion coefficients. The most recent contributions are found in a symposium held by the New York Academy of Sciences (7, 35, 65, 81). The basic theory of molecular diffusion has been treated by Williams and Cady (107) and by Neurath (79) in this Journal and by Duclaux (27). Kincaid, Eyring, and Sterns (60) have contributed a treatment of the kinetics of diffusion, which is especially applicable to diffusion through dense structures such as membranes. Barrer has treated the general subject of diffusion in solids; his book (3) contains two chapters on the diffusion of gases and vapors through organic membranes. The permeability of natural and artificial membranes has been discussed in a symposium of the Faraday Society in 1937 (12, 13, 16, 61, 73, 94, 105) and in the Cold Spring Harbor Symposium of 1940 (49, 58, 66, 68, 82, 83). The literature on permeability has been periodically reviewed in the *Annual Reviews of Biochemistry* through 1937 (14, 51, 52, 57) and since then in the *Annual Reviews of Physiology* (8, 10, 59). Krogh (62) has reviewed numerous cases of the active transport of water and salts between aquatic animals and their environment.

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II. DIFFUSION IN BULK SYSTEMS

A. Thermodynamic considerations

Diffusion is fundamentally a process that equalizes the activities of substances which are free to move in solution. In simple systems substances always diffuse from the higher to the lower activity. While it is possible to set up models in which some components move in the reverse direction from a lower to a higher activity, this can only be done at the expense of energy coming from heat, pressure, an external electrical or gravitational field, or *the diffusion of some other substance* (84). In the absence of activity differences, molecules will still move about but there will be no net movement, since equal quantities will move in opposite directions. It is often possible to represent diffusion between any two concentrations by the algebraic sum of the diffusion from each concentration into pure solvent. Whereas it was at one time popular to talk of membranes with irreciprocal permeability (28, 36, 102, 103) such that a solute could move faster across the membrane in one direction than in the other, the above considerations at once show that diffusion through such a membrane would result in the movement of material from a lower to a higher concentration, a change which requires work. This work in a non-reacting membrane could only come from the heat content of the system, and the system would thus violate the Second Law of Thermodynamics. While it is possible to visualize a membrane containing trap doors of colloidal dimensions which would thus violate the Second Law, no evidence has yet been presented to indicate that such a membrane actually exists.

B. The diffusion coefficient

The diffusion of molecules in solution is described mathematically by Fick's law:

$$\mathrm{d}Q/\mathrm{d}t = DA\ \mathrm{d}c/\mathrm{d}x \tag{1}$$

where Q is the quantity of material which crosses a plane of constant concentration c and area A per unit of time t. D is a proportionality factor, called the diffusion coefficient. As given, Fick's law is just a definition which is useful only because the proportionality factor D is, in many cases, nearly independent of concentration. Since the mathematical treatment of diffusion is greatly simplified by the assumption that D is a constant at a given temperature, D is often called the diffusion constant. Figure 1 shows how D varies with concentration for a number of salts which are of physiological interest. The variations are of the order of 5–30 per cent from infinite dilution up to 1 molar.

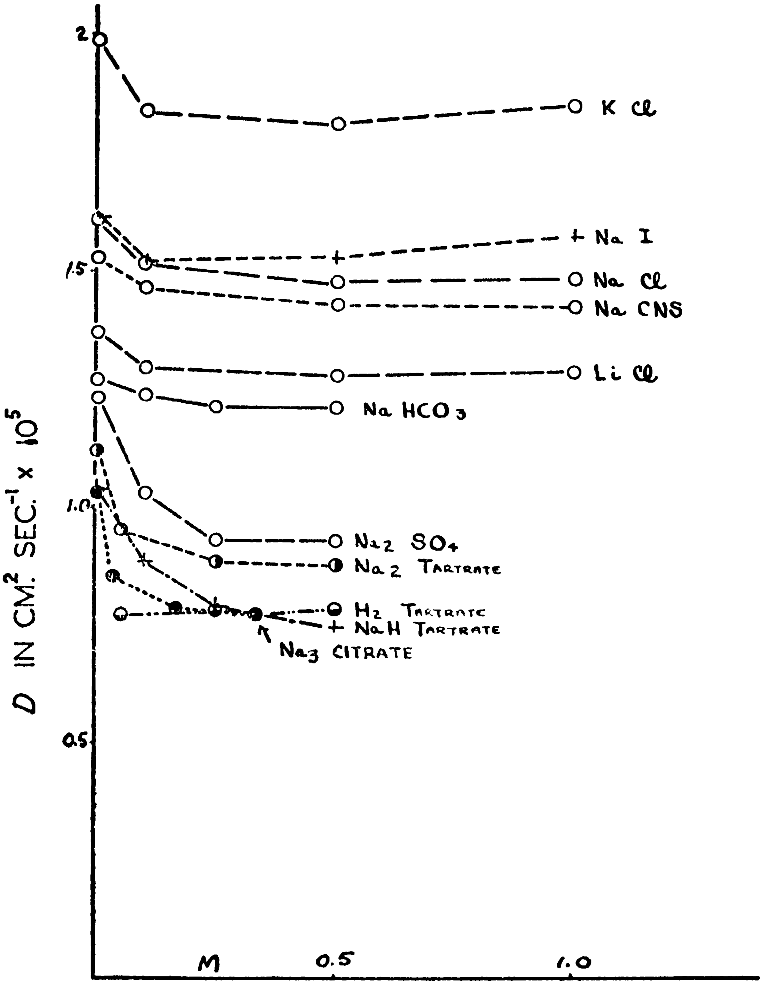

FIG. 1. Diffusion coefficients of some physiologically important electrolytes, recalculated from the data of Vinograd and McBain (99) according to Gordon (35).

When D varies with concentration, the integral diffusion coefficient that is measured is a weighted average of all the diffusion coefficients at all the concentrations through which diffusion is taking place. Nearly all the published values of diffusion coefficients refer to average or integral diffusion coefficients for which the symbol $\bar{D}$ will be used. The relationship between D and $\bar{D}$ is given by

$$D = \bar{D} + c\,\mathrm{d}\bar{D}/\mathrm{d}c \qquad (2a)$$

or

$$\frac{\bar{D}}{c_1 - c_2} = \int_{c_2}^{c_1} D \, \mathrm{d}c \qquad (2\mathrm{b})$$

(65), where c_1 and c_2 are the concentrations between which diffusion is taking place. c_2 is frequently zero. Actual diffusion experiments always produce a change in the concentration of the diffusing substance. The errors introduced by assuming that $\bar{D}$ is actually being measured are negligible unless D is changing rapidly with concentration. Gordon (35) gives a method of successive approximations to determine D from $\bar{D}$ measured in diaphragm cells. When D falls rapidly as the concentration is increased, it can be shown that the integral diffusion coefficient measured in a diaphragm cell will fall more rapidly than the true value of $\bar{D}$. In the case of colloidal electrolytes this can result in negative values for D calculated from $\bar{D}$, if correction is not made for the finite change in concentration during the experiment (23).

Molecules move from one concentration to another because there is a difference of chemical potential μ ($\bar{F}$ of Lewis and Randall) between the two concentrations (44). For ideal dilute solutions of molecules

$$\mathrm{d}Q/\mathrm{d}t = -uRTA \, \mathrm{d}c/\mathrm{d}x \qquad (3)$$

where u is the mobility of the molecule, R is the gas constant, and T is the absolute temperature. Therefore,

$$D = uRT \qquad (4)$$

For ions the Nernst (78) equation for ion movement is

$$\mathrm{d}Q/\mathrm{d}t = -\frac{uA}{z}(RT \, \mathrm{d}c/\mathrm{d}x \pm cxF' \, \mathrm{d}E/\mathrm{d}x) \qquad (5)$$

where z is the valence of the ion without regard for sign, u is the equivalent mobility of the ion, c is the equivalent concentration of the ion, F' is Faraday's constant, and E is the electric field in the direction of diffusion (99). $R = 6.66$ if u is measured in customary electrical units and D in cm.^{2} per second.

In non-ideal solutions, neglecting volume changes,

$$D = -uRT(1 + c \, \mathrm{d} \ln y/\mathrm{d}c) \qquad (6)$$

where y is the activity coefficient (44, 65). The mobility, u, may vary with concentration. As a first approximation

$$u = u_0\eta_0/\eta \qquad (7)$$

where u_0 is the mobility at infinite dilution, η_0 is the viscosity of the solvent; and η is the viscosity of the solution (but see Onsager (81)).

Variations in u may occur for other reasons besides viscosity; one of these is a change in hydration with concentration, which alters the size of the diffusing molecules. For example, discrepancies between calculated and observed diffusion coefficients for sucrose in concentrated solution may perhaps be explained by considering that the water of hydration is greater in dilute solutions than in concentrated solutions (63, 79). Sucrose is, however, an extreme case, and in general the viscosity factor can be trusted to give a slight overcorrection both for diffusion and for conductivity, except in the case of large molecules such as proteins and high polymers (7).

Sutherland (95) and also Einstein (30) equated the osmotic force acting on a diffusing molecule with the resistance to movement of a sphere in a continuous liquid given by Stokes's law. As usually quoted, the so-called Stokes–Einstein equation is

$$D = RT/6\pi r\eta N \tag{8}$$

where r is the radius of the molecule and N is Avogadro's number (79). For molecules which do not obey the ideal gas laws the diffusion coefficient should be corrected by the factor $(1 + c \, d \ln y/dc)$.

In practice for large molecules where the Stokes–Einstein equation applies, the gradient of the activity coefficient is rarely known except for some recent accurate work on carefully purified high polymers (71) and a few measurements on proteins. For small molecules such as sugars, the errors inherent in the derivation of the Stokes–Einstein equation are such that minor corrections for deviations from ideality are insignificant. From a practical point of view, a knowledge of the activity coefficient implies a knowledge of the molecular weight more accurate than can ever be obtained from diffusion data by use of the Stokes–Einstein equation.

It has not been generally noted that the Stokes-Einstein equation applies only to the differential diffusion coefficient D and can be applied to the integral diffusion coefficient $\bar{D}$ only when the diffusion coefficient is a true constant independent of concentration. If the diffusion coefficient varies with concentration, it is best where possible to extrapolate the data to infinite dilution, obtaining D_0, since

$$D_0 = \lim_{c \to 0} D = \lim_{c \to 0} \bar{D} \tag{9}$$

This extrapolation avoids all complications caused by changes in activity and viscosity with concentration, as well as secondary steric effects which may be serious for many high-molecular-weight compounds (7).

In general, even in favorable cases, diffusion measurements alone cannot provide values of the molecular weight to within better than 5 per cent accuracy. They are, however, useful, inasmuch as they are often the only measurements available for substances with biological activity that have not been purified.

C. Measurement of the diffusion coefficient

Longsworth (65) has adequately summarized the various methods available for the measurement of diffusion coefficients in liquids. In the opinion of the author, insufficient consideration has been given to the necessity of eliminating convection currents in diffusion cells. This can be done by the use of thin cells or capillaries of known size for absolute methods. According to the calculations of Young (108), wall effects are not likely to be important at dimensions greater than 10^{-7} cm., so that a refinement of the method of Nakamura (77) or the modification used by Zuber (109) (see also Furth (34)) should give valid diffusion coefficients with a cell thickness of 0.1 mm., which is thin enough to eliminate convection.

The diffusion coefficient in a homogeneous membrane which is bathed on one side by a solution at constant composition can be determined from the time required to reach a steady state (2, 3). This is especially convenient if optical or electrical methods for continuously recording concentration are available. This method is unfortunately not applicable to sintered-glass membranes, because of the presence of cul-de-sacs. The sintered-glass cells introduced by Northrup and Anson (80) must be calibrated by reference to a known substance. McBain's students (99) have used 0.1 N potassium chloride and have calculated a value for $\bar{D}$ at 25°C. from the measurements of Cohen and Bruins (12) at 20°C. of 1.631 cm.^{2}/day, equivalent to 1.888×10^{-5} cm.^{2}/sec. Gordon (35) points out that the value should be 1.838×10^{-5} for the conditions used. In his opinion the method is capable of a relative accuracy of 0.1 per cent, though it must be admitted that deviations of 1 per cent or greater are present in most of the published work.

D. Units of the diffusion coefficient and the diffusion of water

Rashevsky and Landahl (83) have reviewed some of the mathematical aspects of membrane permeability. They point out that the diffusion coefficient should be expressed in cm.^{2} sec.$^{-1}$ instead of in any one of a large number of complicated expressions that have often been used. Diffusion coefficients expressed in cm.^{2}/day should be divided by 86,400 to reduce them to cm.^{2} sec^{-1}. Many people have difficulty at first understanding why the diffusion coefficient is centimeters *squared* per second instead of centimeters per second, since the diffusion coefficient is proportional to the ionic mobility, which is a velocity per unit force. Fick's law (equation 1) can be rewritten as:

$$-D = \mathrm{d}Q \cdot \mathrm{d}x/\mathrm{d}t \cdot \mathrm{d}c \cdot A \tag{1b}$$

Substituting for the quantities their units we obtain for the units of D:

$$D = Q \cdot \text{cm./sec.}\ (Q/\text{cm.}^3)\ \text{cm.}^2 = \text{cm.}^2\ \text{sec.}^{-1} \tag{1c}$$

The quantity transported, Q, may be expressed in any suitable units provided the concentration is expressed in the same units per cubic centimeter. Under these conditions the units of Q will cancel. Diffusion coefficients are usually calculated from the change in concentration of a given volume, and in such cases the units of concentration, whether moles per liter, milligrams per 100 cc., colorimeter readings, rat units per cubic centimeter, or any other, are immaterial so long as they are expressed on a volume basis. Weight normality or weight per cent concentrations are not suitable for use in diffusion calculations. Activity coefficients must also be converted to a volume concentration basis (43).

Water will move through a porous membrane at a rate proportional to the difference in hydrostatic pressure on the two sides of the membrane. If the membrane is semipermeable, water will also move at a rate proportional to the difference in osmotic pressure (or activity of the water) on the two sides of the membrane. The net rate of water movement across a rigid semipermeable membrane is proportional to the difference between the osmotic and the hydrostatic pressures. Eyster (31) has reviewed the definitions that have been used for osmosis and osmotic pressure.

The permeability of a membrane to water is expressed by Krogh (62) by the number of minutes necessary to pass 1 cm.^{3} through 1 cm.^{2} of membrane under a pressure of 1 atm. Lucké (66) expresses permeability in terms of the number of cubic micra crossing a membrane per minute per square micron per atmosphere of difference in osmotic pressure. Both of these units neglect the thickness of the membrane. Rashevsky (83) points out that the correct unit for water permeability is cm. sec. when the thickness is unknown; pressure must be expressed in dynes cm.$^{-3}$ and water movement in grams. If water movement is expressed in cm.^{3}, the units of membrane permeability are cm. dyne^{-1} sec.$^{-1}$ Although it is formally possible to express the osmotic pressure as a difference in molar concentration and determine a diffusion coefficient for water in units of cm.^{2} sec.$^{-1}$ by expressing the water movement in moles, the validity of this formalism is very doubtful, particularly since very few membranes are truly semipermeable.

E. The diffusion of electrolytes

When a salt diffuses, the separate ions formed in solution cannot diffuse independently, although their mobilities may be different. When one ion starts to move ahead of the other because of its higher mobility, the resultant separation of charge produces an electric field which retards the fast ion and accelerates the slow ion, so that both move at the same rate. This electric field appears as the liquid-junction potential whenever a potential is measured between two different solutions.

Vinograd and McBain (99) discuss the diffusion of idealized mixtures of salts. They derive from the classical Nernst equation (equation 5) an exact differential equation for the diffusion of any ion in a mixture of other ions in ideal solution. Their equation has a tractable, integrable form only when the diffusing salts all have linear concentration gradients. Since linear gradients, even if produced artificially, will not persist when more than one salt is diffusing, the integral form must be inexact for real cases. However, it does give a good first approximation that is surprisingly close to the experimental findings. The assumption of linear concentration gradients is incidentally the same assumption made by Henderson (47) to obtain his well-known equation for the diffusion potential.

The integral form of the diffusion equation for one ion in a mixture of salts all diffusing into pure water is,

$$\bar{D}_+ = u_+RT/z\left(1 - z\,\frac{\Sigma m_+c_+/z_+ - \Sigma u_-c_-z_-}{\Sigma u_\pm c_\pm}\right) \tag{10}$$

For anions the minus sign is changed to plus. The symbols have the same meaning as in equation 5. For the purposes of calculation, u and v can as a first approximation be taken from the values at infinite dilution. A better value is obtained from the product of the mean transport numbers and the observed diffusion coefficient of the salts in question. The second term inside the parentheses is the contribution of the electric field set up by the diffusion to the movement of the ion in question. For the diffusion of a single salt, equation 10 reduces to the Haskell equation (46):

$$D = \left(\frac{1}{z_+} + \frac{1}{z_-}\right)RT \Big/ \left(\frac{1}{u_+} + \frac{1}{u_-}\right) \tag{11}$$

Vinograd and McBain (99) apply their equation to the diffusion of mixtures of two salts and compare the experimental and theoretical results. The agreement is very good. The qualitative conclusions are that a cation present in relatively small amount will be accelerated by the accompanying diffusion of a salt with a slower cation than anion and will be retarded by a salt with a faster cation than anion. Conversely for an anion present in small amount. For example they reported that when a mixture of 0.01 N hydrochloric acid and 0.466 N barium chloride diffused into pure water the hydrogen ion had a diffusion coefficient of 9.50 cm.^{2}/day, a value which is 18 per cent greater than the calculated value for the free diffusion of hydrogen ions (8.05 cm.^{2}/day at 25°C.).

When one or more salts are initially at the same concentration throughout the system, the diffusion of other ions is not given by equation 10. If it is assumed that the concentration gradients of the diffusing ions are linear and that the supporting electrolyte (those ions which have no concentration gradient) does not move, it is possible to integrate the differential equation given by Vinograd and McBain (99). Dean (22) obtains the equation:

$$\bar{D} = D_0\left(1 \mp \frac{z\Delta}{\Lambda_s}\left(1 - \frac{\Lambda_0}{\Lambda_s}\ln\left(1 + \frac{\Lambda_0}{\Lambda_s}\right)\right)\right) \tag{12}$$

where $\Delta = \Sigma u_+ c_+/z_+ - \Sigma u_+ c_-/z_-$ for the diffusing salt,
$\Lambda_s = \Sigma u_+ c_+ =$ the conductivity of the diffusing salt, and
$\Lambda_0 = \Sigma u_+ c_+ =$ the conductivity of the supporting electrolyte.

The experimental results are quite close to those predicted by equation 12, in spite of the fact that it is based on approximations. Equation 12 predicts that the effect of a supporting electrolyte will be determined only by its conductivity relative to that of the diffusing salt and will be independent of the relative ionic mobilities of the non-diffusing salt. The supporting electrolyte does actually move in amounts which are of the same order of magnitude as the movement of the diffusing ions. Nevertheless, this movement has a relatively small influence on the movement of the diffusing ions when the supporting electrolyte is present in excess.

When an electric current is applied to a diffusing system, the ions are moved by a summation of electrical and diffusive forces. The current can accelerate or retard the motion of the ions and can even cause a reversal of the direction of movement of some of the ions. In the absence of diffusion the effects are those of Hittorf transport.

Substances normally insoluble in water may be solubilized in detergent solutions to form homogeneous solutions. Solubilization appears to be the result of an association between one or more molecules of the water-insoluble material and colloidal micelles which may contain several hundred detergent molecules. The movement of solubilized materials in solution therefore depends almost entirely on the movement of the corresponding detergent micelles (26). If the detergent is diffusing it will carry the solubilized material with it. When there is no net movement of the detergent, there will still be a slow exchange of micelles full of solubilized material. A membrane such as cellophane, impermeable to micelles but permeable to molecules, may also be permeable to molecules of the solubilized material, which leave their micelles on one side of the membrane and enter new micelles on the other side.

The drag effect of a diffusion stream on other molecules in the medium has been observed by McBain and Dawson (69) and likened to the effect produced by a Langmuir diffusion pump. Young (108) has considered some of the mathematical theory, and Brooks (10) has reviewed recent contributions. In general, the drag effect appears to be a very inefficient mechanism for producing movement of molecules against an activity gradient.

III. DIFFUSION IN MEMBRANES

A. Diffusion of non-electrolytes through membranes

Diffusion takes place in the relatively wide-pored membranes of sintered-glass filters at exactly the same rate as if glass were not there, with the advantage that the diffusion is not disturbed by convection currents (70, 80).

Membranes with small pores, such as collodion, cellophane, parchment, and many biological membranes, greatly slow down or stop the diffusion of large molecules and ions, while offering relatively little resistance to the movement of small particles.[3] This is the so-called sieve effect, which is of practical use in dialysis. For example, if a protein solution containing a salt is placed in a cellophane or Visking sausage skin sack and suspended in running water the small salt ions will diffuse out, leaving all the large protein molecules behind in the sack.

Another important aspect of the permeability of biological membranes is their so-called lipoid solubility. Experimentally it has been found that a large number of cell membranes are more permeable to substances that are soluble in oils than to substances insoluble in oils. The explanation of this phenomenon visualizes the membrane as a separate phase having lipoidal characteristics.

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[3] There has been considerable discussion in the literature with regard to whether highly dried collodion contains pores. There is now agreement that partially dried collodion is a typical porous membrane (88), and since highly dried collodion is practically impermeable to dissolved solutes, the distinction is not of great interest here.

The concentration of the diffusing substance inside the membrane at either boundary will be l times the concentration in the water outside. The partition fraction, l, is defined by the equation:

$$l = \frac{\text{concentration in membrane phase}}{\text{concentration in water}}$$

The rate of diffusion across the membrane is, of course, dependent on the absolute difference in concentration of the diffusing substance inside the two boundaries. Therefore substances which have a high partition fraction, l, will diffuse more rapidly across the membrane. A classical example of this phenomenon is given by a membrane of vulcanized rubber, which is freely permeable to benzene and almost impermeable to water. Benzene is soluble in rubber, whereas water is insoluble in the rubber and can penetrate only through pores or traces of impurities in the rubber.

For many years the sieve theory and the lipoid solubility theory were held by different schools as rival theories explaining the permeability of living membranes. In 1935 Wilbrandt (104) showed that the two theories were not incompatible, and in 1937 Collander (16) summarized a remarkable series of careful diffusion measurements which showed that both molecular volume and lipoid solubility controlled the diffusion of non-electrolytes through a large number of plant-cell membranes.

At about the same time it became apparent from electrical measurements (13) that most vital membranes are extremely thin, perhaps only one or two molecules thick. In such thin membranes the distinction between pores and solubility breaks down and the rival theories appear as different aspects of the same phenomenon.

Fortunately for the mathematical treatment of membrane permeability it makes no difference which theory is used. In a thin membrane diffusion very rapidly reaches a steady state with a linear concentration gradient within the membrane. (The treatment of cases in which the rate of diffusion and mixing in the fluids on the two sides is slow, is outside the scope of this paper. These cases have been discussed by Rashevsky and Landahl (83) and by Barrer (3).) When a steady state has been reached, the amount crossing the membrane in unit time, $\mathrm{d}Q/\mathrm{d}t$, is proportional to the difference in concentration on the two sides.

For diffusion in a collection of pores such as are present in a sintered-glass disk full of water,

$$\mathrm{d}Q/\mathrm{d}t = \bar{D}A'\Delta c/x' \qquad (13)$$

where A' is the effective total cross-sectional area of the pores and x' is the mean length of the pores. Neither A' nor x' is directly measurable, but each may be assumed to be a constant fraction of the corresponding over-all area, A, and the thickness of the membrane, x. Equation 13 can be rewritten

$$\mathrm{d}Q/\mathrm{d}t = DAK'\Delta c/x \qquad (14)$$

where K' is a conductivity factor for the membrane. Since A and x are constant for a given membrane they can be included in the proportionality factor as K, which is then called the membrane constant.

$$\mathrm{d}Q/\mathrm{d}t = DK\Delta c \tag{15}$$

K is determined from the rate of diffusion of a known reference substance, such as 0.1 N potassium chloride (35).

Sieve membranes may consist of pores small enough to reduce the rate of diffusion of large molecules either by having fewer pores large enough to pass the larger molecules or by a wall friction effect. This changes $\bar{D}$ to $\bar{D}'$, a mean diffusion coefficient within the membrane. The actual length of the pores is also unknown, so that the measured diffusion of a given substance is given by

$$\mathrm{d}Q/\mathrm{d}t = \bar{D}'A'\Delta c/x' = hA\Delta c \tag{16}$$

where h is called the permeability of the membrane for the substance in question. Collander (14) compared the permeability coefficients of a series of non-electrolytes in a copper ferrocyanide membrane with the molecular diameter (which is very nearly inversely proportional to the diffusion coefficient in water). He found that the molecular diameters and the permeability coefficients in the membrane were in the inverse order, but that a thirteenfold range of molecular diameters corresponded to a 62-fold range in permeability coefficients. If the pores were all of the same diameter, there would be a sharp cut-off at some definite molecular diameter. The observed range of permeabilities is evidence that there is a range of diameters, so that while relatively few pores can pass large molecules, more pores are available to smaller molecules (32).

In thin lipoidal membranes when diffusion reaches a steady state:

$$\mathrm{d}Q/\mathrm{d}t = \bar{D}Al\Delta c/x \tag{17}$$

Nearly all biological membranes are of unknown thickness and composition, so that l/x must be replaced by another constant K''. Equation 17 can be rewritten:

$$\mathrm{d}Q/\mathrm{d}t = \bar{D}AK''\Delta c/x = hA\Delta c \tag{18}$$

where h is again the permeability of the membrane for the substance in question (83).

All the equations considered in this section reduce to one of the two forms:

$$\mathrm{d}Q/\mathrm{d}t = \bar{D}'A\Delta c/x \tag{19}$$

or

$$\mathrm{d}Q/\mathrm{d}t = hA\Delta c \tag{20}$$

$\bar{D}'$ is the integral diffusion coefficient of the diffusing substance in the membrane and h is the permeability coefficient. The permeability coefficient h equals $\bar{D}'/x$ and is especially useful when the thickness of the membrane cannot be measured.

When membranes have appreciable thickness and the solutions on both sides are well stirred, the time, L, for diffusion to reach a steady state is given by equation 21 (2, 3):

$$L = x/6h = x^2/6\bar{D}' \qquad (21)$$

B. Diffusion of electrolytes through membranes

All the conditions controlling the diffusion of non-electrolytes through membranes, as well as the conditions controlling the diffusion of electrolytes in bulk solution, apply to the diffusion of electrolytes in membranes that contain no indigenous ions. In general, either or both ions may suffer changes in their relative diffusion mobility, owing either to the different medium or to pores small enough to hinder the ions. Neutral oil layers are good examples of homogeneous uncharged non-reacting membranes, while cellophane or very pure collodion is a fairly good approximation to uncharged pore membranes. Very little work has been done on these systems, because absolutely isoelectric solid membranes have not been available (see, however, 75) and also because of the greater interest in the large and striking effects which are obtained when electrolytes diffuse through ionized membranes or oils which contain ionizing molecules.

Beutner (5, 6) carried out a long series of experiments in which he measured the electrical potentials set up when electrolytes diffuse through oils containing acidic or basic dissolved substances (37). Osterhout (82) followed up these oil-membrane experiments, doing most of his work with guaiacol, an acidic phenol. He measured actual transport in some cases as well as the potentials produced.

An oil membrane can be set up between two aqueous layers, for example, by placing a heavy oil at the bottom of a U-tube with different concentrations of potassium chloride solution in the two arms. If identical calomel electrodes are placed in the two potassium chloride solutions, there will be a potential difference between these two electrodes. The more dilute potassium chloride solution will be positive if an acidic oil such as guaiacol is used, and negative if a basic oil such as aniline is used. Beutner (5, 6) ascribed these results to phase-boundary potentials, while Bauer (4) and later Ehrensvärd and Sillén (29) ascribed the results in some cases to adsorption on the interface. Dean (19, 20, 24) pointed out that, at equilibrium, adsorption could not influence potentials and that the potential effects could all be explained by the diffusion of the solute, or one of its ions, into the oil phase, producing both phase-boundary and liquid-junction potentials. In the case of potassium chloride and guaiacol, the potassium ion forms potassium guaiacolate and can diffuse across the guaiacol as such, while the chloride ion and the hydrochloric acid formed by hydrolysis are practically insoluble and cannot diffuse in the oil layer. The guaiacol therefore behaves as a membrane permeable only to cations. Aniline, on the other hand, behaves as a membrane only to anions, since chloride ions are soluble in aniline as aniline hydrochloride, and potassium ions and potassium hydroxide are not soluble in aniline.

When a membrane separates two different concentrations of the same electrolyte, the potential difference produced is given to a fair degree of approximation by the well-known Nernst equation (78):

$$E_1 - E_2 = \frac{u - v}{u + v} \frac{2.3RT}{F} \log c_1/c_2 \tag{22}$$

where $E_1 - E_2$ is the difference in potential between the two solutions. $2.3RT/F$ has the value 0.059 volt at 25°C. u and v are the effective mobilities of the ions in the membrane. Equation 22 can be written in the more general form:

$$E_1 - E_2 = -\frac{RT}{F}\left(\int_{c_2}^{c_1} t_+/z_+ \,\mathrm{d} \ln c_+ - \int_{c_1}^{c_2} t_-/z_- \,\mathrm{d} \ln c_-\right) \tag{23}$$

where t_+ and t_- are the transport numbers of the cation and anion, respectively. This is a useful form when the concentrations of the two ions in the membrane are different but the activity coefficients are constant over the concentration range. Equation 23 is a special case of the general equation given by Guggenheim (41). When the concentration c_1 is ten times c_2, the maximum potential difference that can be obtained is 59 millivolts at 25°C. This can occur if the membrane is completely impermeable to one ion so that t_+ (or t_-) $= 0$ or u (or v) $= 0$.

Since potential measurements are relatively so easy to make, numerous workers (including the author (18)) have interpreted measurements on membranes as indicative of permeability to ions by means of equation 23 (for examples see 76, 82). It must be pointed out that this equation is only valid: (*a*) when the diffusing ions penetrate all the way through the membrane; (*b*) when no other ions, stored or being produced in the membrane, are diffusing out; and (*c*) when the membrane consists of one homogeneous medium. Conditions (*b*) and (*c*) are not often realized for biological membranes, and conditions (*a*) and (*b*) are often not satisfied for highly impermeable synthetic membranes.

When a membrane exhibits the maximum thermodynamic potential difference because only cations or only anions can penetrate, there can be no diffusion through the membrane in the absence of an external circuit to remove the charge carried by the diffusing ions. In general, the more closely the potential of a membrane approaches to the theoretical maximum the more nearly impermeable it is to the diffusion of salts.

Although a guaiacol membrane should not allow potassium chloride to diffuse from a higher to a lower concentration, it will allow potassium ions to exchange for sodium ions if such a membrane separated potassium chloride from sodium chloride. The guaiacol (symbol HG) dissociates as an acid to form G^- and H^+ ions. K^+ and Na^+ are soluble in guaiacol and can diffuse either as ions with G^- as the gegen ion, or they can diffuse as undissociated KG and NaG. Osterhout (82) assumes that potassium and sodium diffuse as undissociated molecules, but some diffusion of the free ions probably occurs also, since guaiacol saturated with water and potassium chloride is a reasonably good electrical conductor.

Solid membranes that have bound ions in their pores have been investigated potentiometrically by Meyer and his coworkers (73, 75) and later by Marshall and Bergman (72). A theoretical treatment of the potentials produced was developed independently by Meyer *et al.* and by Teorell (96). Fetcher (33) showed that the potentials actually observed by Meyer *et al.* do not agree quantitatively with those that would be predicted from their theoretical equations, and the discrepancies have been further explained by Sollner and Carr (92). Qualitatively, however, ionized porous membranes are of great interest and diffusion through them may produce striking results, as has been shown by Sollner and coworkers (89, 90).

The term "charged membrane" is a misnomer, as a membrane cannot maintain a static charge in a conducting solution. The term "charged membrane" (like the term "charged colloid") is applied to membranes that contain fixed ions of one charge combined with water-soluble ions of the opposite charge. "Charged" membranes might better be called ionic membranes. The sign of the charge on the membrane is the sign of the bound ions. The bound ions may be adsorbed on the surface of the pores, or they may be chemically combined with the substance of the membrane. An example of the first type is provided by the positively charged permselective membranes of Sollner (1, 39). These membranes are made by the adsorption of protamine cations on nitrocellulose membranes. The second type is exemplified by oxidized nitrocellulose membranes (38), where oxidation has produced carboxyl groups presumably on the sixth carbon atom of the glucose residues (89). These carboxyl ions will be accompanied by an equivalent number of sodium gegen ions. When such an oxidized membrane is set up between two solutions of sodium chloride of different concentration, the membrane will be more permeable to sodium than to chloride ions, because the concentration of sodium ions inside the pores is greater than the concentration of chloride ions. The concentration is greater because sodium ions must be present to balance the bound carboxyl ions as well as the diffusible chloride ions. When the membrane is bathed in sufficiently dilute solutions, nearly all the mobile ions in the membrane will be sodium ions and the membrane will behave electrically as if it were a connected pair of electrodes reversible to sodium ions. The membrane will also be almost impermeable to sodium chloride if the pores are sufficiently small. Obviously, the concentration of bound ions in the membrane and the pore size will control the ratio of sodium ions to chloride ions in the membrane for any given concentration of sodium ion outside. Membranes that have small pores and a high ratio of bound ions to pore volume will produce nearly the maximum thermodynamic electrical potentials and will likewise be nearly impermeable to the diffusion of salts.

If a cell is completely enclosed by a uniform membrane and a potential difference exists across this membrane, the potential cannot of itself produce any movement of ions. Such movement can only occur when a current flows, and in order that current may flow the potential must have different values in different parts of the cell surface.

If a current flows through a membrane which bears ions on its surface, there will be a movement of the solution through the membrane. This flow is known as electroösmosis or electroendosmose (9) and will be in the same direction as the movement of those ions which balance the ions on the membrane. Electroosmosis can be considered to be the direct result of the drag of the gegen ions on the columns of solvent in the pores. In bulk solutions the drag produced by cations is exactly equal and opposite to the drag produced by the anions. In a pore, however, one type of ion cannot be moved, because it is attached to the wall of the pore and the drag of the gegen ions on the solution is unopposed. The magnitude of the effect is proportional to the fraction of the current in the pore which is carried by the gegen ions. Consequently, electroösmosis is decreased by increasing the electrolyte content of the system.

IV. ACTIVE TRANSPORT THROUGH MEMBRANES AGAINST CONCENTRATION GRADIENTS

Diffusion, so far, has been discussed only from the standpoint of ideal systems where diffusion transports material from a higher to a lower concentration. There are many other cases, particularly in living systems, where transport of material takes place from the lower to the higher concentration. Indeed, life as we know it would be impossible if living systems did not have the ability to do this "osmotic work." However, there are no proven cases where inanimate systems have been demonstrated as capable of causing *all* solutes to move against their activity gradients at constant temperature.

The minimum thermodynamic work ΔF required to move material in solution from one concentration to another at constant pressure and temperature is given by

$$\Delta F = \Delta NRT \ln (a_1/a_2) \tag{24}$$

where ΔN is the number of moles of material moved, a_1 is the activity at the concentration from which the substance is moved, and a_2 is the activity at which the substance is delivered. When several constituents change in activity, the work term is the sum of the work terms for each substance.

Equation 24 shows that work will be done when a substance diffuses from a higher to a lower activity and that work is required to move a substance from a lower to a higher activity. For ordinary dilute systems the activity is closely proportional to the concentration. That is, $a = c\gamma$, where c is the concentration and γ is the activity coefficient, which often does not differ greatly from unity.

Although the activity usually follows the concentration, there are cases where diffusion is caused by changes in activity at constant concentration. An example of this is given by the *diffusion retrograde* of Thovert (45). In one experiment a solution of potassium chlorate in water was separated from a solution of potassium chlorate of equal concentration in a mixture of acetone and water. Acetone of course diffused into the aqueous solution, but in addition potassium chlorate diffused into the aqueous solution, although it was initially at the same concentration in the two systems. The movement of potassium chlorate took place because it had a higher activity in the acetone–water mixture than in pure water. This is demonstrated by the fact that its solubility is much less in acetone–water mixtures than in pure water. Conversely, if a substance proportionately more soluble in acetone, such as acetanilide or butyric acid, had been used, the movement would undoubtedly have been in the opposite direction. Thovert's *diffusion retrograde* therefore is a case of spontaneous diffusion occasioned by differences in the activity coefficient of the substance at the same concentration. Schreinemakers (84, 85) has discussed numerous examples of anomalous concentrations set up while diffusion is taking place.

The movement of ions initially at the same concentration throughout can easily be produced by setting up an electrical field. The electrical field can in turn be produced by the diffusion of a suitable salt, preferably though not necessarily through a membrane.

Among examples of this type of "up hill" diffusion are many experiments of Osterhout (64, 82), where the constant diffusion of carbon dioxide (as carbonic acid) produces accumulation of potassium ion or chloride ion in one or another chamber. Teorell (97) has presented a theory of this movement and has set up an experiment where the constant diffusion of perchloric acid, constantly added to a small chamber containing a solution of ammonium chloride in contact through a membrane with a large vessel of the same concentration of ammonium chloride, produced an increase in the ammonium-ion concentration and a decrease in the chloride-ion concentration inside the membrane. In this case, as in most cases of its type, there was no increase in the product of the concentrations of the two ions moved. The system is exactly analogous to that occurring when a Donnan equilibrium is set up between two systems one of which contains a non-diffusible ion. In Teorell's experiment the concentration of perchlorate ion was artificially maintained by the constant addition of perchloric acid. No simple system of this sort can concentrate both cations and anions simultaneously.

Although modifications of the Donnan equilibrium cannot increase the activity product of a cation and an anion at the same time, there is at least one result of diffusion through membranes which could lead to accumulation of salts. Ingraham, Peters, and Visscher (53) proposed a fluid circuit theory, in which a solution was pumped around a circuit containing a membrane impermeable to one of the solutes. The non-penetrating solute would be accumulated in the chamber behind the membrane. This mechanism in its original form merely shifted an uncertainty about the mechanism for concentrating the solute to an uncertainty about the mechanism for moving the solution as a whole. A mechanism capable of moving the solution was not postulated. Sollner and coworkers (40, 87, 89) have demonstrated and explained one mechanism whereby diffusion across a membrane can produce large movements of the solution, which may be in the direction of natural osmotic flow but more rapid than normal or may be opposed to this flow. This phenomenon is known as anomalous osmosis and is termed negative (anomalous) osmosis if the fluid movement is initially from the more concentrated to the more dilute solution. Negative osmosis is one mechanism which might produce the flow of fluid required by the fluid circuit theory if some electrolyte were supplied continuously to one chamber and removed as rapidly as it diffused into the other chamber. According to Grollman and Sollner (40), negative osmosis can occur when the electrical potential set up in one membrane (or one part of a membrane) is sufficient to produce electroosmotic flow through another membrane in circuit with it. The two membranes might be only pores of different character or dimensions in the same membrane. If, for example, one membrane consisted of small pores lined with negative ions and consequently permeable only to positive ions, there would be a potential set up by any cation which was more concentrated on one side of the membrane than the other. The side having the lower concentration would be positive. If the second membrane had large pores which were lined with positive ions, this potential would cause current to flow and some of the current would be carried as an electroösmotic stream from the more dilute to the more concentrated solution. Variations of this phenomenon permit negative osmosis in membranes bearing the same charges on all pores if the ions have very different mobilities (87). Since proteins are amphoteric it is not hard to imagine a membrane with some pores containing excess cations while other pores contain excess anions. If one set of pores is larger than the other, negative osmosis must accompany the diffusion of an electrolyte through the membrane. The identification of the diffusing electrolyte presents some difficulties, however. Ingraham and Visscher (55) suggested that the production of ammonia in the gut and its diffusion into the blood stream where its concentration is held at a very low level by the activity of the kidneys might provide the necessary electrolyte. Although electrokinetic phenomena are in general reduced by high salt concentrations, anomalous osmosis is shown to the greatest degree by solutions of the order of 0.02 *N* (89) and the effects are still strong at 0.16 *N*, a concentration which is in the physiological range. Although Sollner's work shows that anomalous osmosis might provide a mechanism for the active transport of electrolytes under rather special conditions, there is as yet no positive evidence that such a mechanism actually operates *in vivo*.

Other mechanisms for active transport which are of a somewhat similar nature postulate the formation of a compound between the solute being transported and some constituent of the membrane. The compound is then supposed to diffuse through the membrane and liberate the original solute on the other side. Specifically, Wilbrandt and others (61, 67, 98, 106) have proposed a mechanism to move glucose out of the kidney tubules or the intestine by the formation of glucose phosphates and their subsequent hydrolysis in or near the blood stream.

Brooks (11) has reviewed several theories of ion-accumulation mechanisms which depend on the production of an electrolyte inside the cells which by its outward diffusion causes ionic accumulation in the cell. He particularly favors a mosaic membrane having adjacent regions of cation and anion permeability and what appears to be a one-for-one ion exchange through these regions. For example, in a cation-permeable region each hydrogen ion coming out would do so by exchanging for one potassium ion going in, while in a nearby anion-permeable region each bicarbonate ion coming out would bring in one chloride ion• The carbonic acid which diffuses out would be supplied by the respiration of the cell. This mechanism cannot be effective in tissues with low respiratory rates, where the moles of carbon dioxide produced are less than the moles of salt accumulated. Another similar mechanism involves cation exchange for ammonium ions.

Wells (101) proposed a mechanism whereby the continuous formation of an osmotically active substance in a cell would produce fluid flow through a series of membranes.

Many examples of anomalous permeability occur in physiological literature. For example, dyes are often found to be much more concentrated in certain cells than in the surrounding fluid. This is often a case of sorption or precipitation of the dye inside the cell, which fixes its activity and permits more dye to come in (37). However, there are undoubtedly cases where secretory or excretory organs concentrate dyes (and other substances) without precipitating them or otherwise significantly altering their activity coefficients (54). Another experiment which has caused some confusion is the observation by Wertheimer (102, 103) that dyes penetrate frog skin more rapidly in one direction than the other. Eckstein (28) has shown that in the case of dyes such effects may occur in the early stages of an experiment without involving active transport. Differences in the dye uptake of the two sides of the membrane are adequate to explain the observations. Nevertheless, Krogh (61) has shown that frogs can actively transport sodium chloride from tap water into their plasma. Even after all the spurious cases of apparent active transport have been accounted for (and all cases of apparent active transport without a continuous supply of energy in non-living systems have been so accounted for), there still remains a vast collection of undoubted cases where living systems do perform osmotic work. These range from the uptake of salts from very dilute spring water by fresh water algae to the excretion of a concentrated urine by land animals (50, 62). Virtually all cells have contents which differ in concentration and activity from the surrounding fluid, and all such cells must obtain their contents at the expense of osmotic work. Only a minute fraction of the many types of active uptake have been adequately explained (for example, the concentration of oxygen in fish bladders (56)). We know only that the general respiration of the tissue responsible in every case that has been tested is many times greater than the osmotic work accomplished (21, 23, 93). A complete list of proven examples of active osmotic work is outside the scope of this review. The most that can be done is to point out the universality of the phenomenon and our general ignorance of its mechanism.

Mention should be made of the use of radioactive or other isotopes as a tool for investigating permeability (42, 48, 86). By the use of radioactive potassium ions it has been possible to show that potassium is continuously moving in and out of red blood cells at a rate much too slow for measurement by conventional methods (25). It has also been possible to trace the movement of water, sodium ions, and chloride ions both out of and into the gut during the active absorption of sodium chloride and water (100). The advantages of this method stem from the fact that radioactive isotopes do not alter either the ionic composition of the fluids or the metabolism of the organism when used in normal doses. It is therefore possible to find out the actual magnitude of ionic movements even under static conditions. For example, since the red blood cell maintains its potassium content in the face of a continuous leak to the blood plasma, it must be continuously expending energy to pump the potassium back in again.

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THE CHEMISTRY OF THE MONOCYCLIC α- AND γ-PYRONES

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[1] Present address: Sloan-Kettering Institute for Cancer Research, New York, New York.

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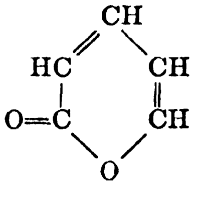
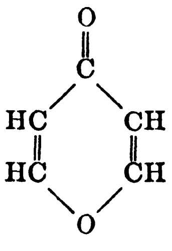
I. INTRODUCTION

The pyrones belong to the class of six-membered heterocyclic compounds containing an oxygen atom. An inspection of the formulas of the α- and γ-pyrones



α-Pyrone



γ-Pyrone

reveals that a functional similarity exists between these ring systems. α-Pyrone possesses a lactonic structure, while γ-pyrone is the vinylog of a lactone; indeed, many of the chemical properties of these nuclei are similar. It must be emphasized, however, that the γ-pyrone nucleus represents a more complex ring system. The anomalous chemical behavior of this nucleus has obscured its exact nature, and the problem of structure has become one of classical interest.

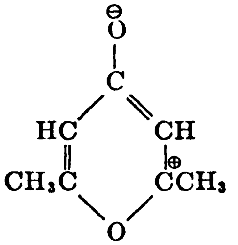
The present review will be concerned only with the chemistry of the monocyclic α- and γ-pyrones. Since the chemistry of the γ-pyrones has been of greater general interest, it will be discussed first.

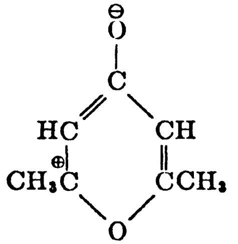
II. γ-PYRONES

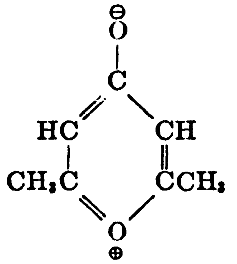
A. STRUCTURE

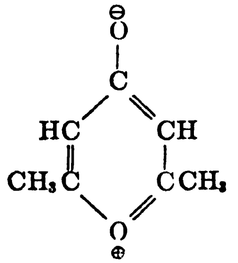
The γ-pyrone nucleus contains three types of functional groups joined together in such a manner as to give rise to a ring system which possesses a set of chemical properties quite unlike those of any of its component groups. The carbonyl group does not react with hydroxylamine, phenylhydrazine, or semicarbazide to produce an oxime, a phenylhydrazone, or a semicarbazone, respectively. Addition of halogens or halogen acids does not take place across the carbon–carbon double bond. Stable crystalline oxonium salts are formed on treatment with acids, indicating that γ-pyrones are unusually strong oxygen bases. This anomalous behavior has caused a great deal of uncertainty in assigning a detailed structure to the γ-pyrone ring (15, 28, 29, 38, 41, 50, 54, 58, 81, 117, 143, 144, 203, 260, 261).

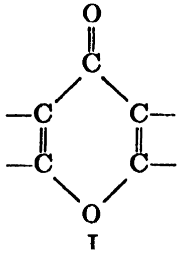
Physical data have clarified to some extent the question of structure. Dipole moment measurements (120, 139, 207, 248) require that various resonance forms (3, 5, 6, 7, 115, 147, 217) make major contributions to the actual state of the molecule. These resonance forms are in better agreement with the chemical properties of γ-pyrones than a simple ketonic structure (I). However, parachor deter-







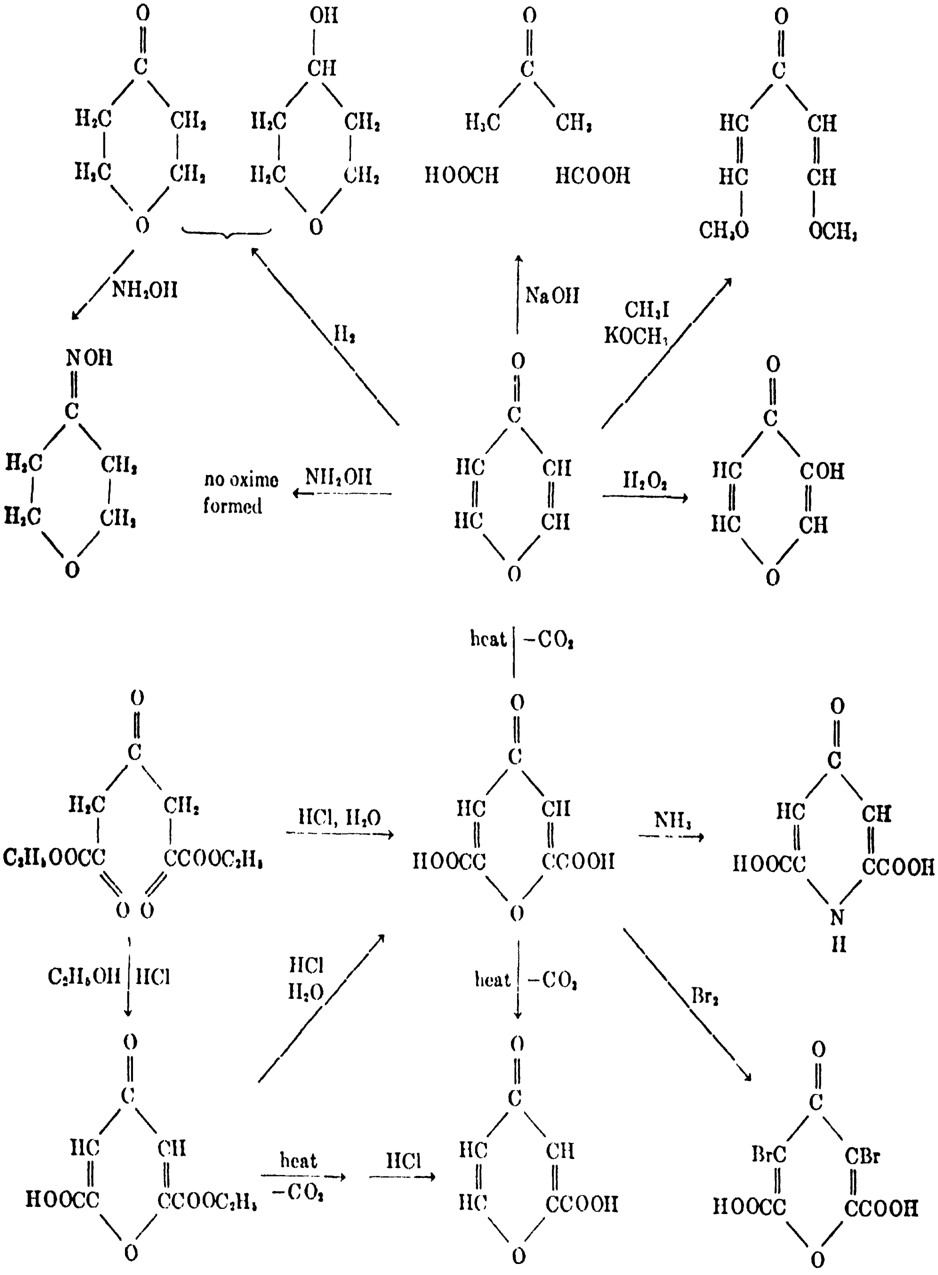




I

TABLE 1

Interconversions in the γ-pyrone series



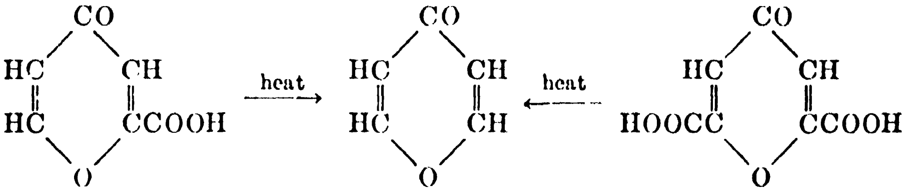
minations (72) and ultraviolet absorption spectra studies (96, 112, 209) indicate that structure I also contributes to the state of the molecule. No single structure, therefore, is adequate to express the true state of the γ-pyrone ring.

B. PREPARATION

Various interconversions which are typical of γ-pyrones are illustrated in table 1.

1. γ-Pyrone

From comanic acid or chelidonic acid: The decarboxylation of either comanic (II) or chelidonic (III) acid leads to the formation of γ-pyrone (106, 169, 259).



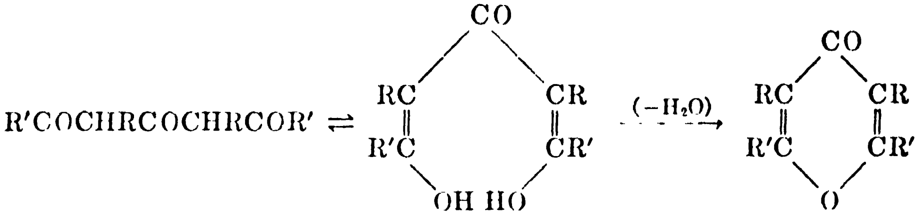
II
Comanic acid

III
Chelidonic acid

The decarboxylation takes place more smoothly in the presence of copper powder (260, 261).

2. Substituted γ-pyrones

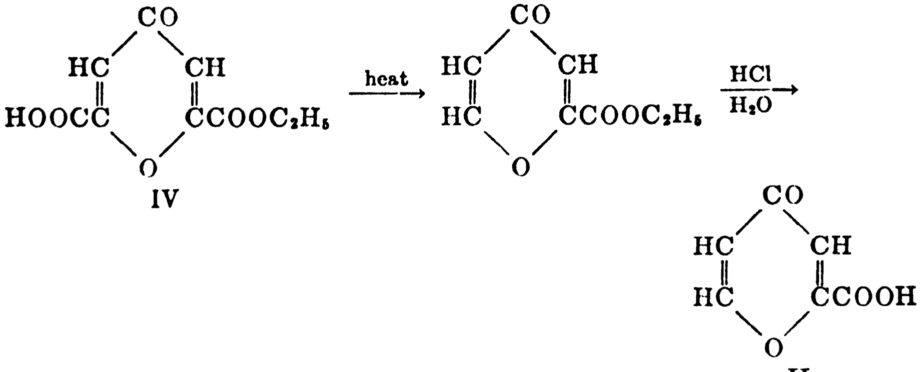
In general, substituted γ-pyrones are prepared by cyclization of the appropriate open-chain keto derivative.



R, R′ = alkyl, aryl, carbethoxyl.

(a) Carboxylic acids

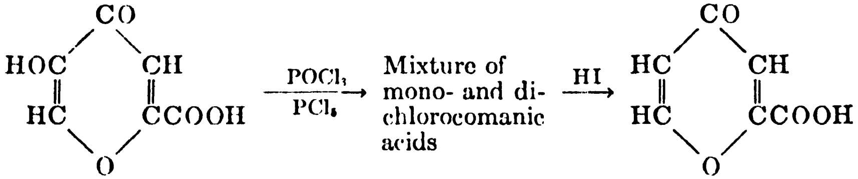
Comanic acid, pyrone-2-carboxylic acid (II): Small quantities of comanic acid are formed by the decarboxylation of chelidonic acid (108). This method has the main disadvantage that the major product of the reaction is γ-pyrone. A more suitable method for the preparation of comanic acid is found in the decarboxylation of monoethyl chelidonate (IV) (42).



IV

II
Comenic acid

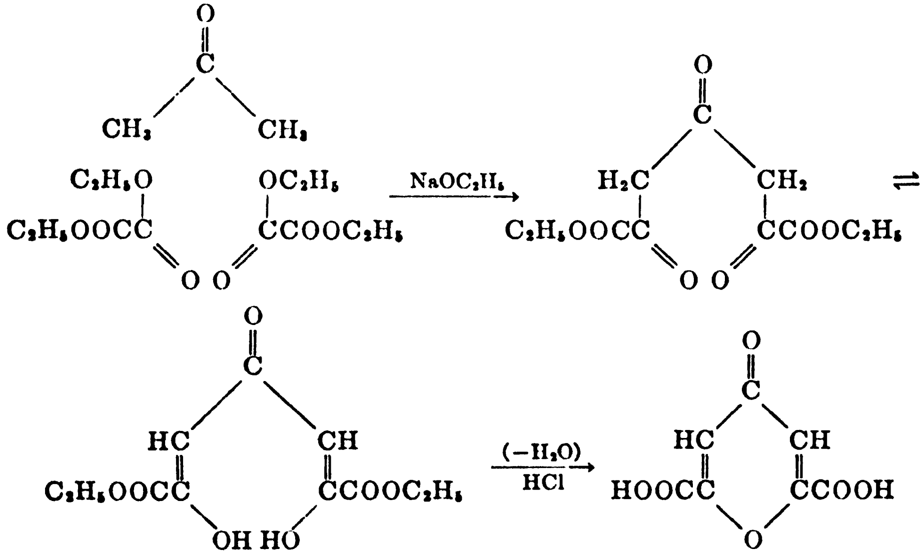
Comanic acid may also be obtained from comenic acid (V) by treatment with a mixture of phosphorus pentachloride and phosphorus oxychloride and subsequent reduction of the reaction mixture with hydriodic acid (168).



V
Comenic acid

II

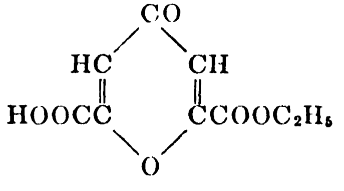
Chelidonic acid, pyrone-2,6-dicarboxylic acid (III): Chelidonic acid occurs in



III
Chelidonic acid

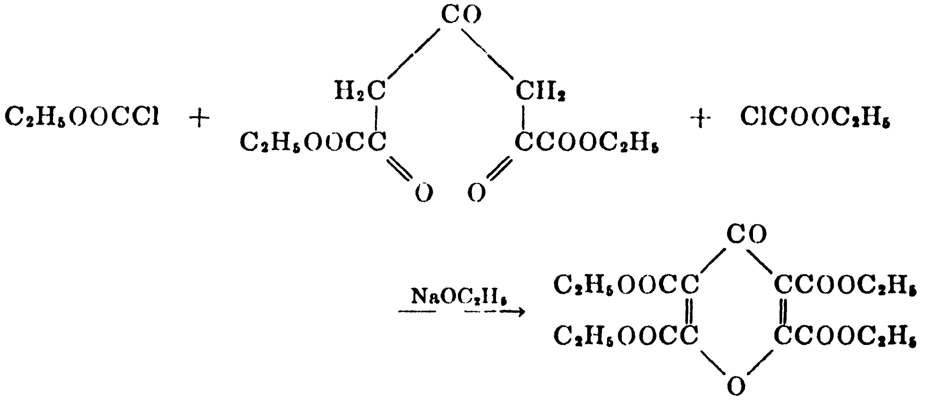
nature in celandine (*Chelidonium majus*) (201, 206), *Polygonatum officinale*, *Polygonatum multiforum* (136), *Asparagus officinalis* (205), and in the alkaloids of white hellebore (*Veratrum grandiflorum* Loes. fil.) (223).

It is prepared by the treatment of acetonedioxalic acid ethyl ester with aqueous hydrochloric acid (42, 50, 106, 140, 141, 201, 259, 260, 261). If this ester is treated with alcoholic hydrogen chloride containing a small quantity of water, monoethyl chelidonate (IV) is produced in good yield (42).



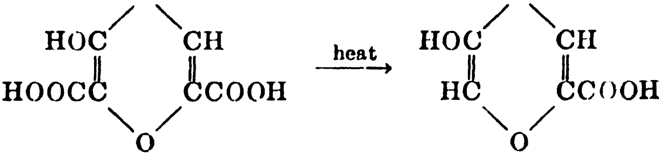
IV

γ-Pyrone 2,3,5,6-tetracarboxylic acid ester (VI): The reaction of ethyl chloroformate with acetonedioxalic ester leads to the formation of the ester VI (189).



VI

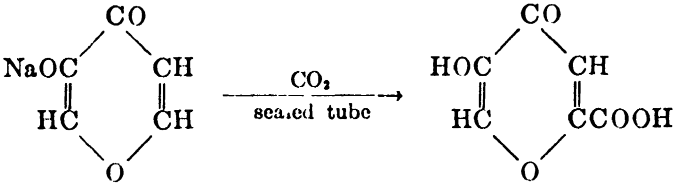
Comenic acid, 5-hydroxypyrone-2-carboxylic acid (V): Comenic acid is produced in nature when acetic acid bacteria (isolated from fruit) act on galactose (237, 238). It may be prepared by the decarboxylation of meconic acid (VII) either



VII
Meconic acid

V
Comenic acid

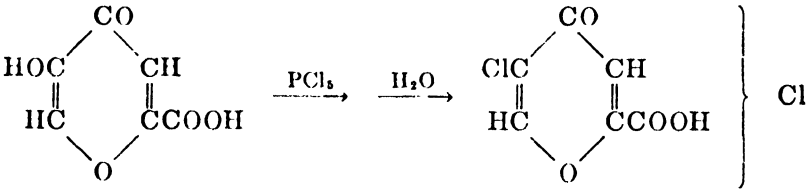
in the presence of copper powder (31, 118, 119, 153, 165, 187, 212, 214, 215, 234, 245) or in boiling aqueous hydrochloric acid (31, 75, 154). It is formed in low yield by the action of carbon dioxide on the sodium salt of pyromeconic acid (VIII) (186). This reaction calls to mind the Kolbe synthesis of salicylic acid from sodium phenoxide and carbon dioxide.



VIII Pyromeconic acid

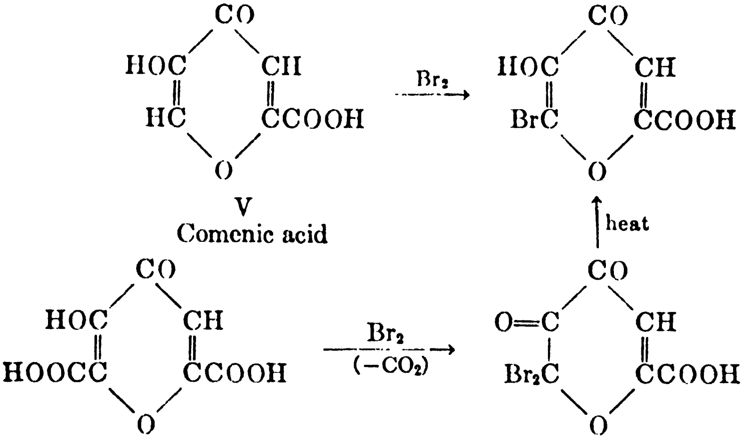
V Comenic acid

Treatment of comenic acid with phosphorus pentachloride results in the formation of a dichloro compound of unknown structure (167).



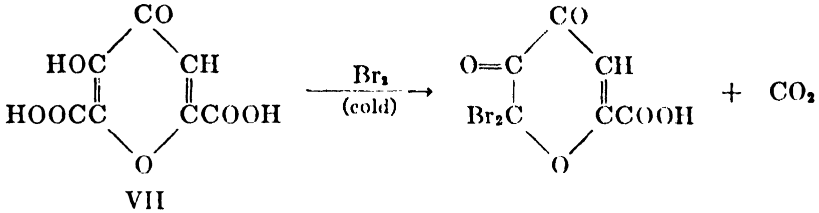
V

6-Bromocomenic acid: 6-Bromocomenic acid is prepared by the bromination of either comenic acid (V) (166) or meconic acid (VII) (119). In the case of meconic acid the reaction is carried out at elevated temperatures and the di-bromo acid first formed decomposes to produce some of the monobromo acid.



VII
Meconic acid

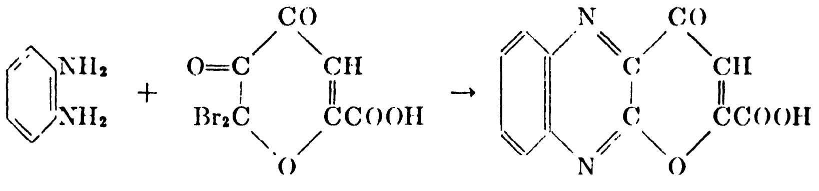
6,6-Dibromocomenic acid: The reaction of bromine and meconic acid (VII) at low temperatures results in the decarboxylation of meconic acid with subsequent formation of 6,6-dibromocomenic acid (153).



VII

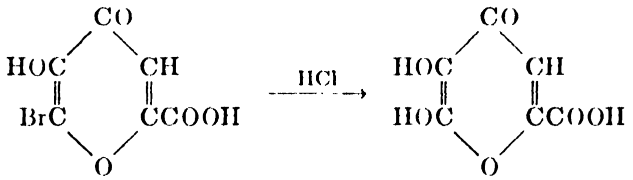
Meconic acid 6,6-Dibromomeconic acid

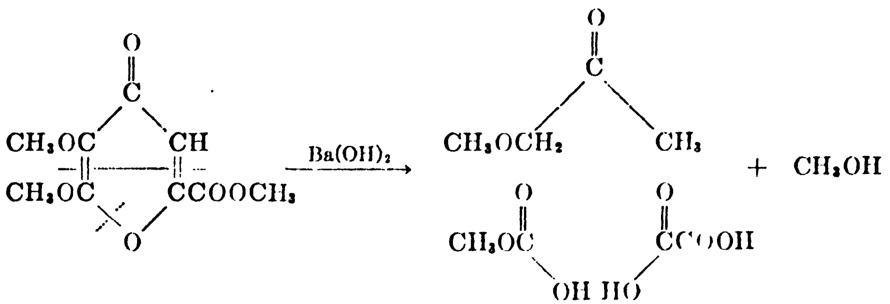
The interaction of dibromocomenic acid with *o*-phenylenediamine produces the quinoxaline IX (180). Dibromocomenic acid may be reduced to monobromocomenic acid with zinc and mineral acids (152).



IX

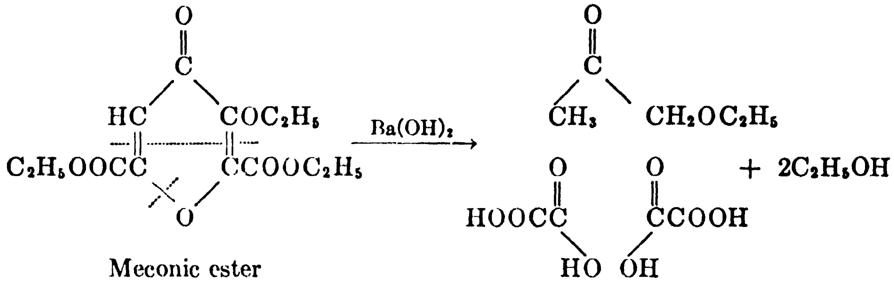
6-Hydroxycomenic acid: 6-Hydroxycomenic acid is prepared by the hydrolysis of 6-bromocomenic acid with either aqueous hydrochloric acid (166) or barium hydroxide (208). The prolonged action of barium hydroxide on the dimethyl ether of 6-hydroxycomenic acid results in complete degradation (183).



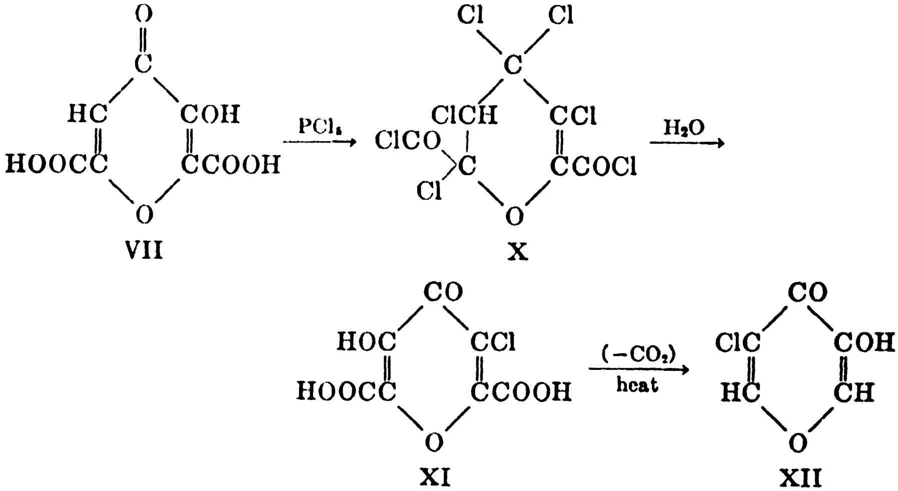


Meconic acid, 3-hydroxypyrone-2,6-dicarboxylic acid (VII): Meconic acid occurs in opium (99, 210, 211, 213, 228), but it does not contribute to the physiological activity of this substance (1, 138).

The structure of meconic acid was demonstrated by the identification of the alkaline degradation products formed with barium hydroxide (22, 142, 145, 146, 184, 191, 241, 249).


Meconic ester

Treatment of meconic acid (VII) with phosphorus pentachloride yields a dicarboxylic acid chloride containing five atoms of chlorine (X). Digestion of this acid chloride with water produces a dibasic acid (XI) which may be completely decarboxylated to the compound XII (116). Compounds X, XI, and XII have not been characterized, but the following sequence would appear likely.

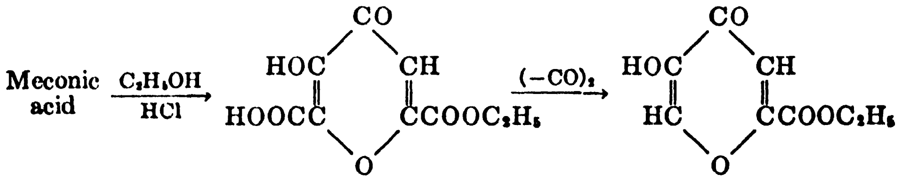

VII

X

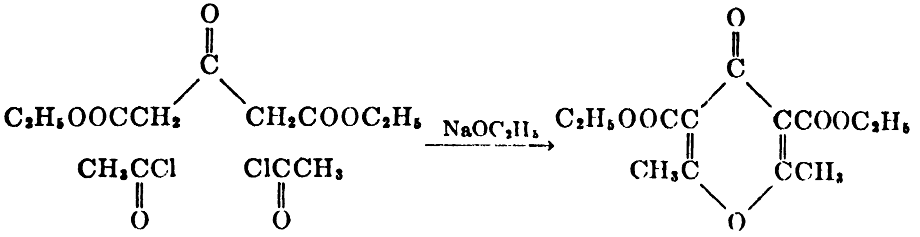
XI

XII

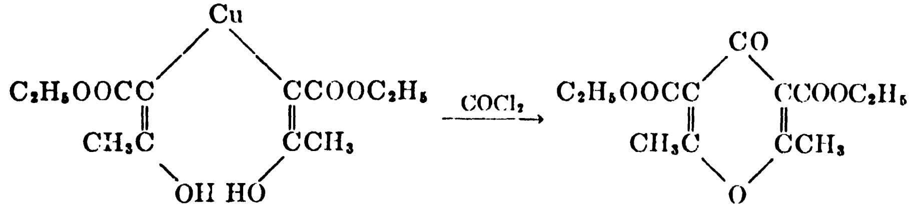
Meconic acid may be esterified to the mono acid ester in good yield by means of absolute alcohol and hydrogen chloride (152). Decarboxylation of this ester results in the formation of ethyl comenate.


Ethyl comenate

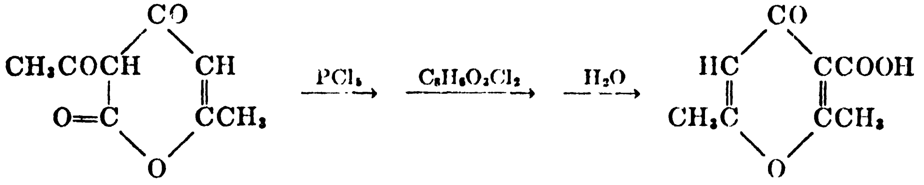
Ethyl 2,6-dimethylpyrone-3,5-dicarboxylate: The preparation of ethyl 2,6-dimethylpyrone-3,5-dicarboxylate may be carried out by treating diethyl acetonedicarboxylate with acetyl chloride (189).



Treatment of the copper salt of acetoacetic ester with phosgene also leads to the formation of ethyl 2,6-dimethylpyrone-3,5-dicarboxylate (64, 246).



2,6-Dimethylpyrone-3-carboxylic acid: Treatment of dehydroacetic acid (XIII) with phosphorus pentachloride results in the formation of 2,6-dimethylpyrone-3-carboxylic acid (55, 57, 81, 164).

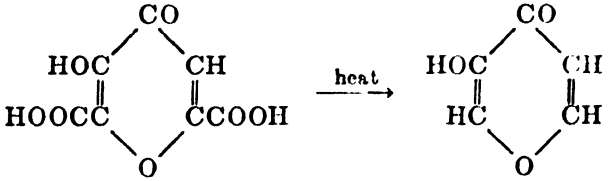


XIII
Dehydroacetic acid

The intermediate chloro derivative has not been characterized.

(b) Hydroxy-γ-pyrones

Pyromeconic acid (VIII): Pyromeconic acid is prepared by the complete decarboxylation of meconic acid (VII) (31, 37, 121, 165, 185, 186, 234). Small

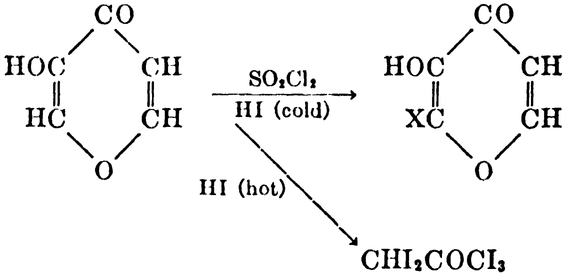


VII
Meconic acid

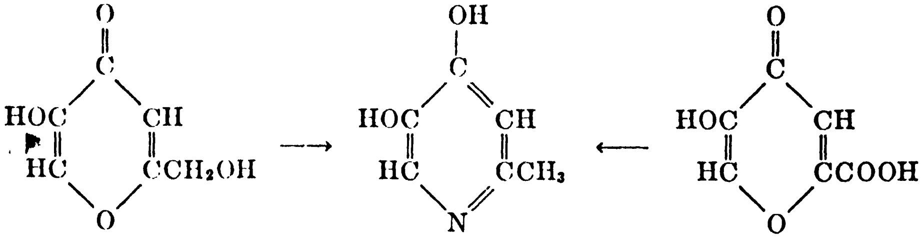
VIII
Pyromeconic acid

quantities (2 per cent) of pyromeconic acid are formed by the oxidation of γ-pyrone with hydrogen peroxide in the presence of sulfuric acid and ferrous sulfate (181).

Halogenating agents react with pyromeconic acid (VIII), resulting in the formation of the 6-halogeno derivative (183, 193, 194). The reaction with hot hydriodic acid leads to the formation of pentaiodoacetone.

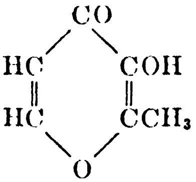


Kojic acid, 5-hydroxy-2-hydroxymethylpyrone (XIV): Kojic acid[2] is formed by the action of the fungus *Aspergillus flavus* on xylose or dextrose (159). The conversion is of interest, since in the case of xylose a five-carbon-atom compound is transformed into a six-carbon-atom compound. Proof of the structure of kojic acid is seen in the following conversions:



XIV
Kojic acid

Maltol, 3-hydroxy-2-methylpyrone (XV): Maltol is found widely distributed



XV
Maltol

in nature. It occurs in the vapors of roasting malt (36), in the branches of the larch tree (190, 235), and in fresh needles of the silver fir (90). It may be obtained by the dry distillation of cellulose (79), from the acid hydrolysates of soybeans (129), and as a product of the alkaline hydrolysis of streptomycin (224).

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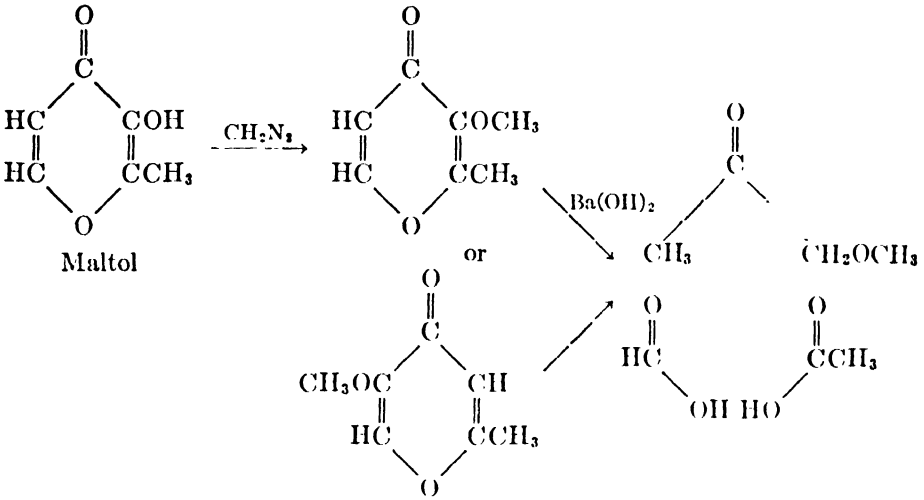
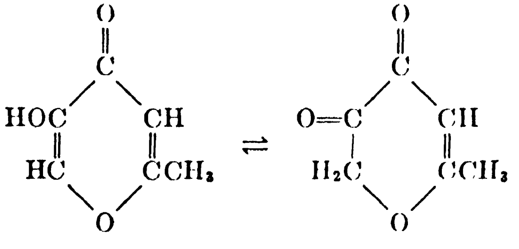
[2] An extended discussion of kojic acid has been omitted, since a review article has already appeared in the literature (18).

Characterization of maltol was accomplished by means of degradation studies (194).



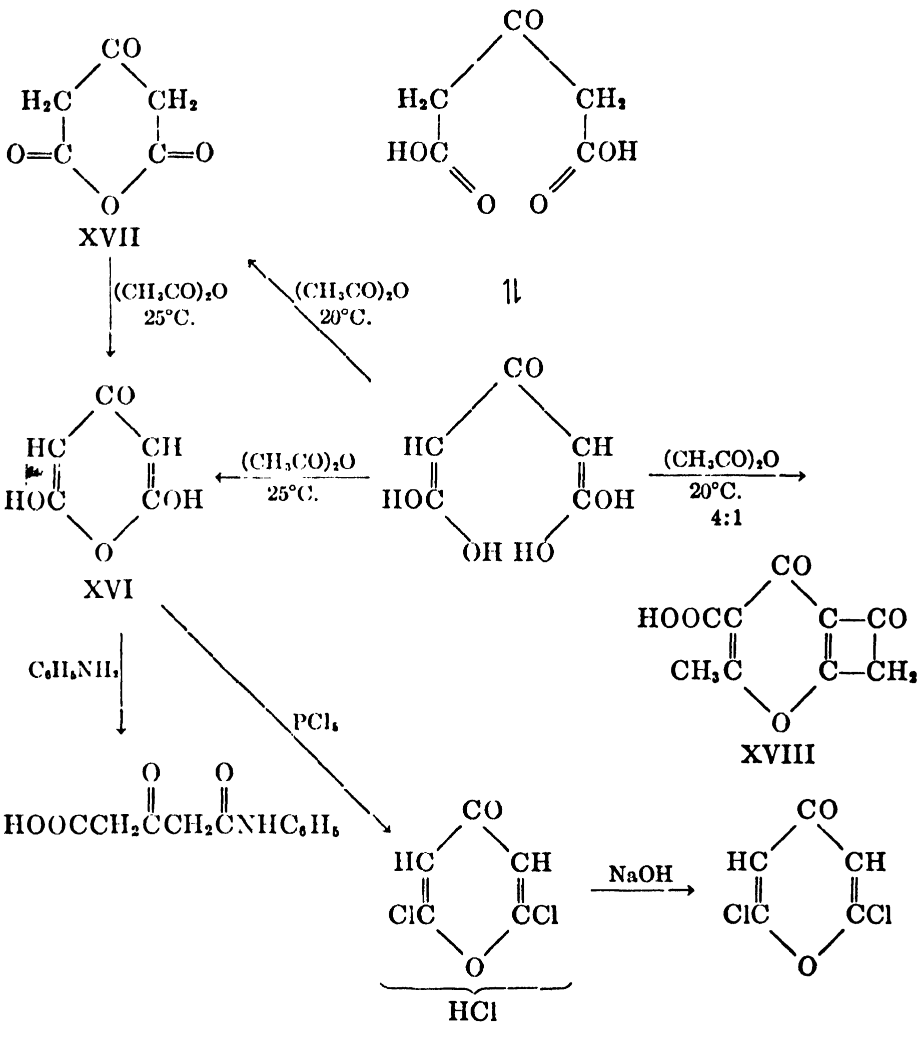
The possibility that maltol is 5-hydroxy-2-methylpyrone rather than 3-hydroxy-2-methylpyrone was ruled out on the basis of the following evidence: Maltol reacts neither with ethyl nitrite to produce an oxime nor with sulfuryl chloride to produce a chloro derivative. These reactions would be expected to take place if maltol possessed the following structure:



The absence of these reaction products, therefore, indicates that the position adjacent to the hydroxyl group is substituted.

2,6-Dihydroxypyrone: When acetic anhydride is caused to react with acetonedicarboxylic acid at 25°C., 2,6-dihydroxypyrone (XVI) (the enol form of acetonedicarboxylic acid anhydride) is produced, m.p. 94°C. At temperatures less than 20°C. the keto form (XVII) is formed, m.p. 136°C. When the ratio of acetic anhydride to acetonedicarboxylic acid is 4:1, compound XVIII is produced (124). The keto form (XVII) may be converted to the enol form (XVI) by treatment with acetic anhydride at 25°C. 2,6-Dichloropyrone may be prepared by the action of phosphorus pentachloride on 2,6-dihydroxypyrone (XVI).

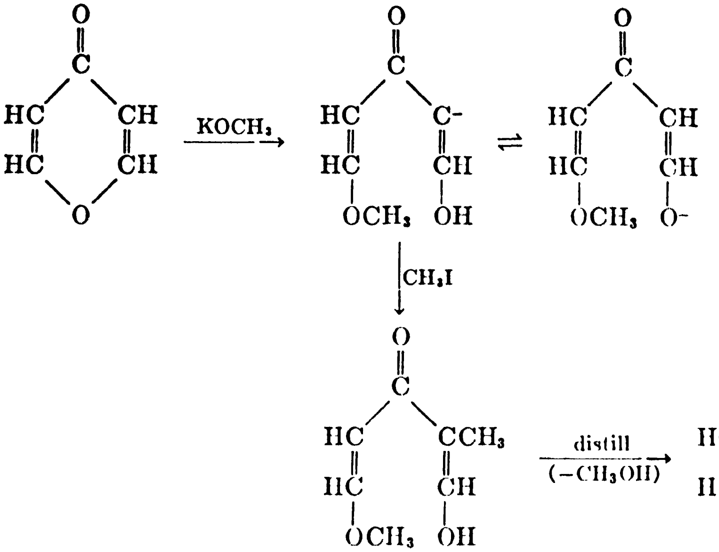
The treatment of XVI with aniline results in the formation of the monoanilide of acetonedicarboxylic acid (125).



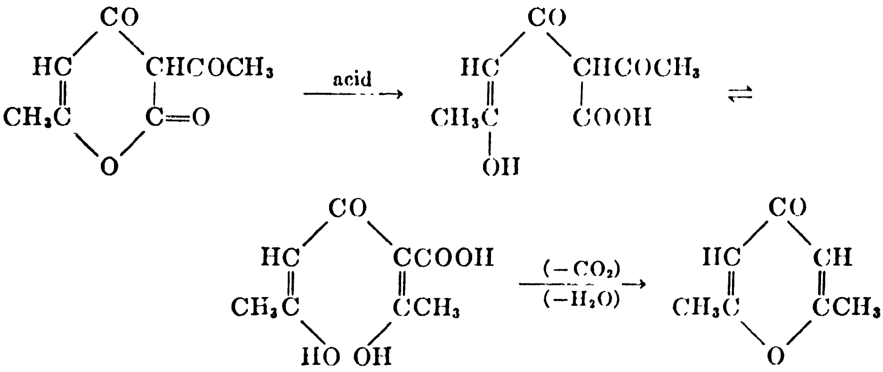
3-Hydroxy-2,6-dimethylpyrone: 2,6-Dimethylpyrone may be oxidized to 3-hydroxy-2,6-dimethylpyrone by the action of hydrogen peroxide in the presence of sulfuric acid and ferrous sulfate (243). This oxidation is analogous to that encountered with γ-pyrone itself.

(c) Alkyl-γ-pyrones

3-Methylpyrone: 3-Methylpyrone is formed when methyl iodide reacts with γ-pyrone in the presence of potassium methoxide (261).

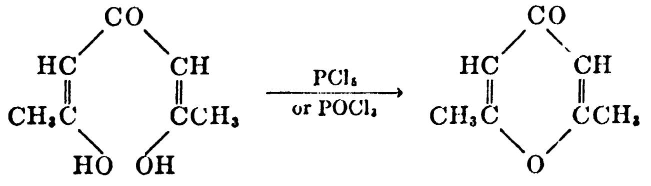


2,6-Dimethylpyrone: 2,6-Dimethylpyrone may be prepared from dehydroacetic acid by the action of either sulfuric, hydrochloric, or hydriodic acid (52, 53, 81, 82). The reaction takes place according to the following equations:

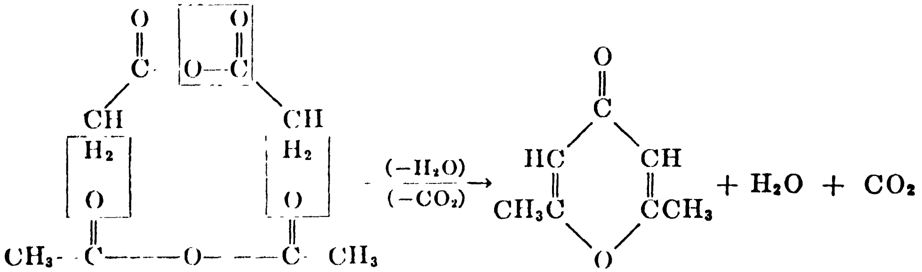


2,6-Dipropylpyrone is similarly prepared from dehydropropionylacetic acid (71).

Diacetylacetone may be cyclized with either phosphorus pentachloride or phosphorus oxychloride to yield 2,6-dimethylpyrone (89).

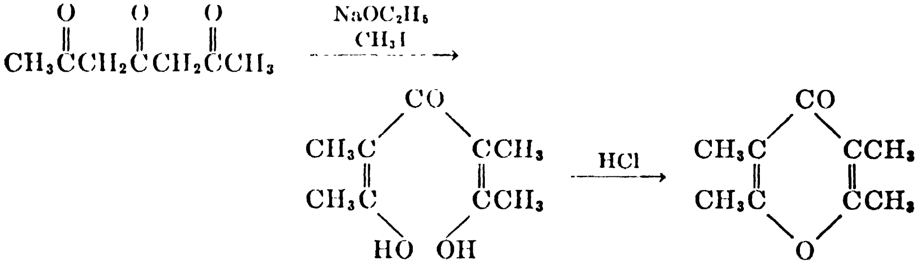


Skraup and Priglinger (232) made the interesting discovery that acetic anhydride is converted to 2,6-dimethylpyrone in low yield (2 per cent) in the presence of either phosphorus pentoxide or concentrated sulfuric acid.

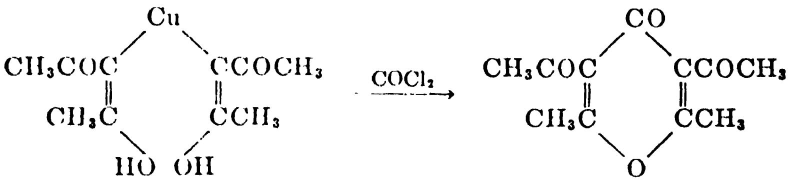


The addition of acetone to the reaction mixture increases the yield of 2,6-dimethylpyrone to 4 per cent (198). In the presence of ethyl methyl ketone, 2,3,6-trimethylpyrone is formed.

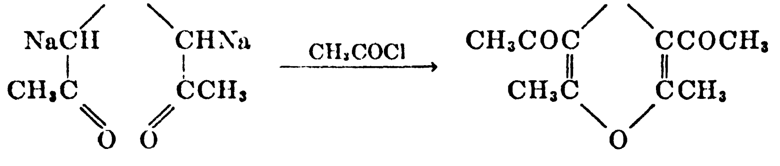
2,3,5,6-Tetramethylpyrone: 2,3,5,6-Tetramethylpyrone is prepared by the action of hydrochloric acid on dimethyldiacetylacetone (58). If ethyl iodide is substituted for methyl iodide in this reaction, a mixture results which is composed of 2,6-dimethyl-3-ethylpyrone and 2,6-dimethyl-3,5-diethylpyrone (14).



3,5-Diacetyl-2,6-dimethylpyrone: 3,5-Diacetyl-2,6-dimethylpyrone is formed when phosgene reacts with the copper salt of acetylacetone (244).

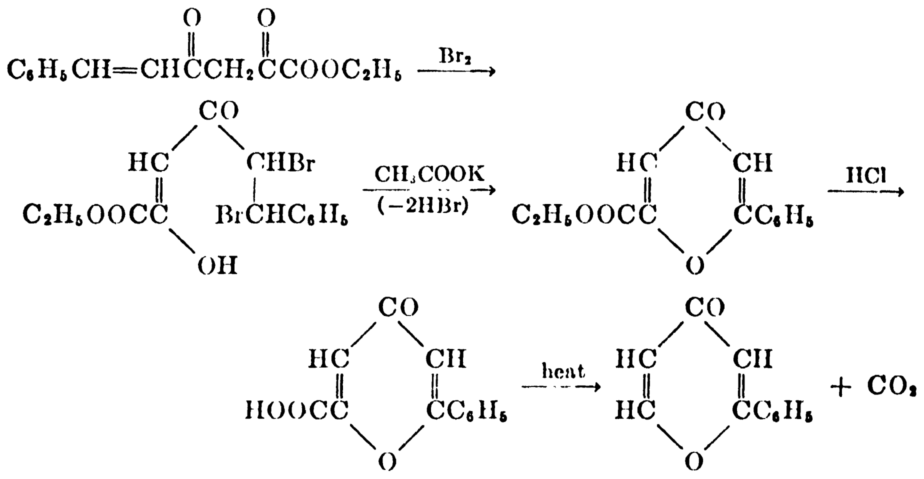


3,5-Diacetyl-2,6-dimethylpyrone may also be prepared by the action of acetyl chloride on the disodium salt of diacetylacetone (54).

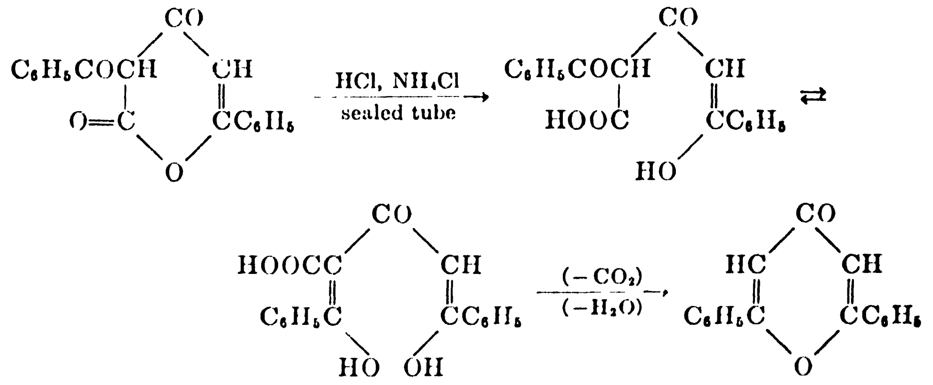


(d) Aryl-γ-pyrones

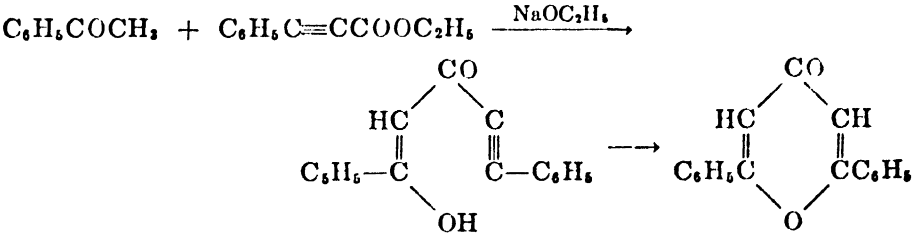
2-Phenylpyrone: 2-Phenylpyrone is prepared by the action of potassium acetate on ethyl cinnamoylacetate dibromide (33).



2,6-Diphenylpyrone: The preparation of 2,6-diphenylpyrone from dehydrobenzoylacetic acid (227) is analogous to that of 2,6-dimethylpyrone from dehydroacetic acid.



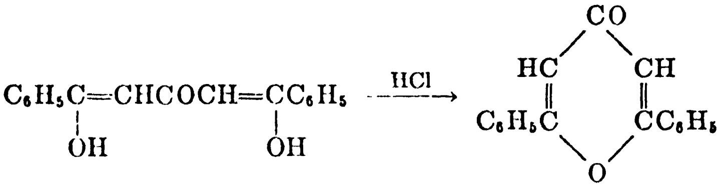
The reaction of acetophenone with ethyl phenylpropiolate yields 2,6-diphenylpyrone (49).



2,6-Diphenylpyrone may also be prepared by the action of alcoholic potassium hydroxide on dibenzalacetone tetrabromide (251).

$$C_6H_5CH{=}CHCOCH{=}CHC_6H_5 \xrightarrow[CHCl_3]{Br_2}$$

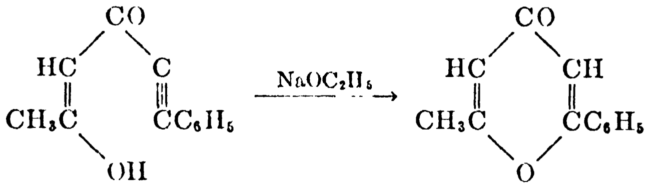
$$C_6H_5CHBrCHBrCOCHBrCHBrC_6H_5 \xrightarrow[(-2HBr)]{\text{alc. KOH}}$$



2-Phenyl-6-methylpyrone: 2-Phenyl-6-methylpyrone is prepared by reacting acetone with ethyl phenylpropiolate in the presence of sodium ethylate (17, 219).

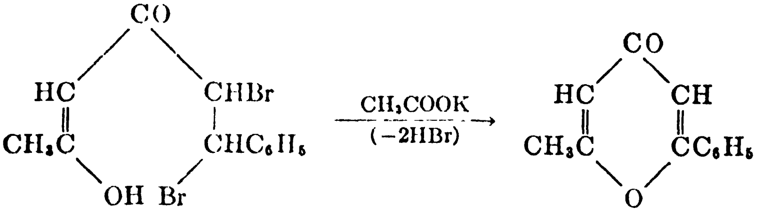
$$CH_3COCH_3 + C_2H_5OOCC{\equiv}CC_6H_5 \xrightarrow{NaOC_2H_5}$$

$$CH_3COCH_2COC{\equiv}CC_6H_5 \rightleftharpoons$$



2-Phenyl-6-methylpyrone may also be prepared by the action of potassium acetate on cinnamoylacetone dibromide.

$$C_6H_5CH{=}CHCOCH_2COCH_3 \xrightarrow{Br_2} C_6H_5CHBrCHBrCOCH_2COCH_3 \rightleftharpoons$$



(e) Halogenated γ-pyrones

Halogenated γ-pyrones may be produced by direct halogenation of either the γ-pyrone ring or the appropriate open-chain compound. The former method is discussed on page 563.

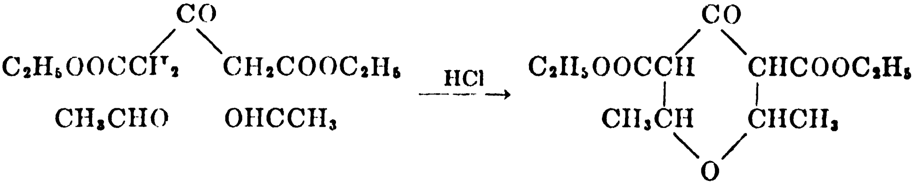
The action of bromine on acetonedioxalic ester results in the formation of diethyl 3,5-dibromochelidonate (88). If chlorine is used in place of bromine, decomposition occurs and a considerable quantity of oxalic acid and chloroacetones is formed together with a small quantity of the desired diethyl 2,6-dichlorochelidonate. A higher yield of diethyl 2,6-dichlorochelidonate may be obtained by the use of sulfuryl chloride; in this case, however, the product is contaminated with the monochloro derivative (86). Iodination of acetonedioxalic ester does not produce an iodopyrone.

Treatment of the barium salt of diacetylacetone with selenium tetrachloride results in the formation of 3,5-dichloro-2,6-dimethylpyrone (158).

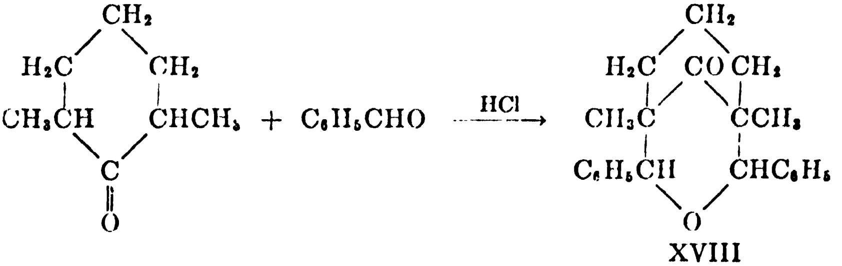
3. *Hydropyrones*

Hydropyrones resulting from either the catalytic hydrogenation or the chemical reduction of the γ-pyrone nucleus will be discussed on page 551. We shall be concerned here only with the hydropyrones which are formed directly.

Hydropyrones may be prepared by an aldol reaction in either acid or alkaline solution. For example, the reaction of acetaldehyde with diethyl acetonedicarboxylate in the presence of aqueous hydrochloric acid leads to the formation of ethyl 2,6-dimethyltetrahydropyrone-3,5-dicarboxylate (196, 222). Diethyl ketone condenses with benzaldehyde in aqueous sodium hydroxide to yield 2,6-diphenyl-3,5-dimethyltetrahydropyrone (196). The action of 40 per cent formaldehyde on acetone in alkaline solution produces small quantities of 3-(or 5-)-hydroxymethyltetrahydropyrone (156).



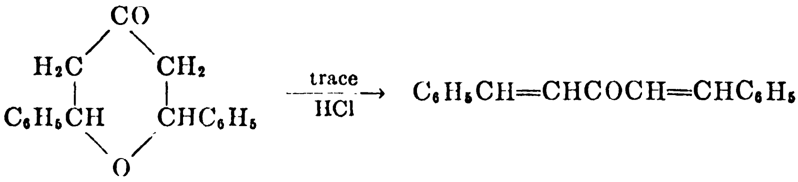
The reaction is not limited to open-chain carbonyl compounds. Cornubert (66, 67) obtained tetrahydropyrones from cyclic ketones.



XVIII

Compound XVIII would be expected to have four optically active forms existing as two *d,l* racemic modifications, together with four *meso* forms. Cornubert isolated three forms: A, m.p., 175°C.; B, m.p., 216°C.; C, m.p., 206°C. A and B are obtained from *cis*-2,6-dimethylcyclohexanone, while C results from the action of hydrochloric acid on A.

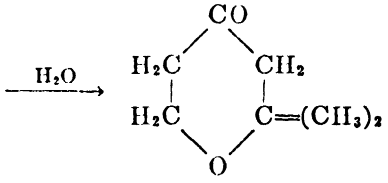
Treatment of diphenyltetrahydropyrones with aqueous hydrochloric acid at high temperatures (125–150°C.) results in the formation of a variety of hydrolysis products, from which only benzaldehyde has been isolated (66). In the presence of traces of hydrochloric acid the degradation is incomplete. Thus, dibenzalacetone is produced when hydrochloric acid acts on 2,6-diphenyltetrahydropyrone (68).

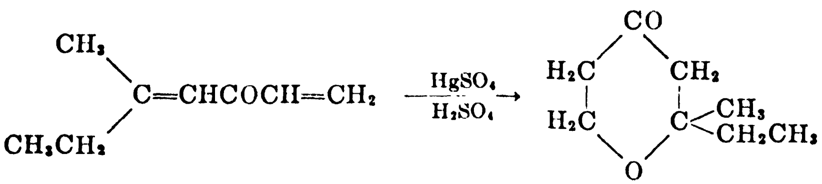


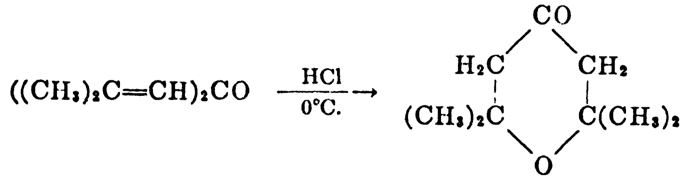
Attempts to reduce the carbonyl group in tetrahydropyrones with sodium and alcohol have been unsuccessful (79). The oxidation of 2,6-diphenyltetrahydropyrone with potassium permanganate results in the formation of formic, benzoic, oxalic, and carbonic acids.

Hydropyrones may also be prepared by the isomerization and subsequent hydration of the appropriate unsaturated carbinols (77, 78). For example, (dimethylvinyl)ethynylcarbinol is isomerized to dimethylvinyl vinyl ketone by the action of mercuric sulfate and sulfuric acid. The divinyl ketone is hydrated and then undergoes cyclization to 2,2-dimethyltetrahydropyrone. The intermediate unsaturated ketone need not be isolated; in fact, unsaturated ketones may be used as the starting materials (161).

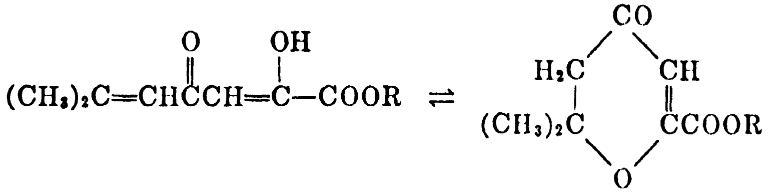
$$(CH_3)_2C{=}CHCHOHC{\equiv}CH \xrightarrow[H_2SO_4]{HgSO_4} (CH_3)_2C{=}CHCOCH{=}CH_2$$







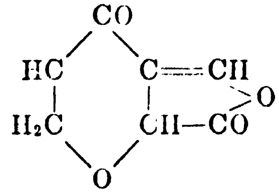
The formation of dihydropyrones by the isomerization of the appropriate monovinyl ketone presents an interesting case (9, 34, 73, 92, 130). The enol form of XIX exists in equilibrium with the cyclic dihydro derivative XX. The equilibrium lies far to the right.



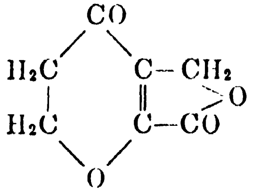
XIX (3 per cent)

XX (97 per cent)

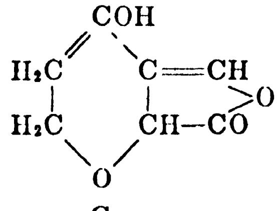
Clavacin: Clavacin (patulin) is a tetrahydropyrone derivative which has been isolated from culture media of *Aspergillus clavatus* (253) and *Penicillium claviforme* (20). According to Raistrick (204), clavacin may be considered to be the lactone of 3-hydroxymethylenetetrahydrocomanic acid (structure A). However, Bergel and coworkers (21) have presented evidence that clavacin exists in solution as a mixture of isomers, and suggested the forms A, B, C, and D.



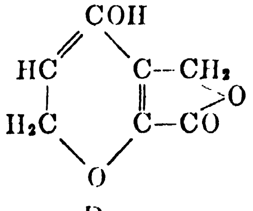
A



B

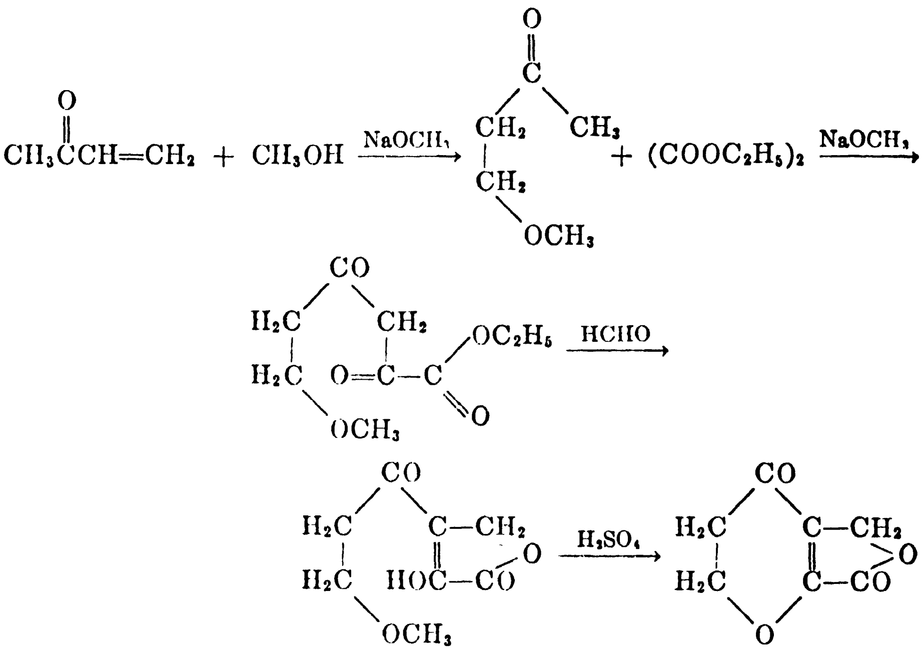


C



D

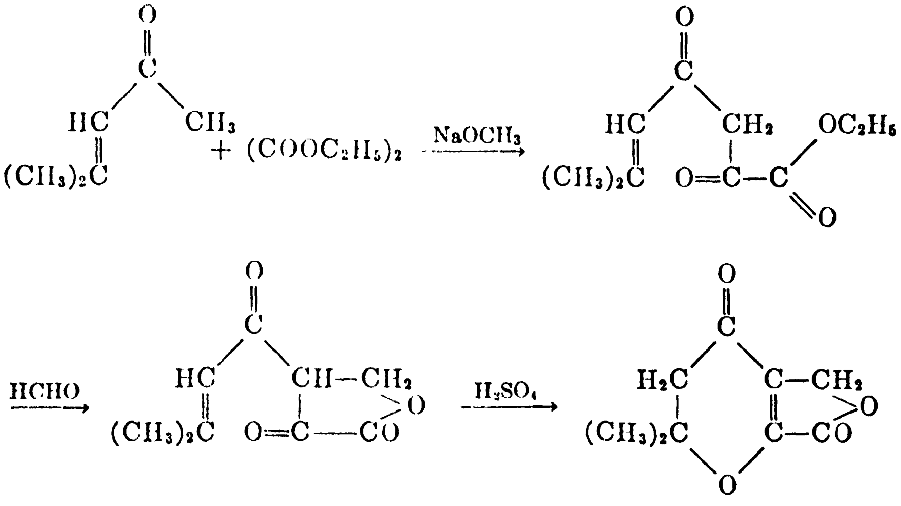
The isomer B has been synthesized by Puetzer, Nield, and Barry (202) by the reactions shown. It does not exhibit the characteristics of clavacin and may be eliminated from the list of possibilities.



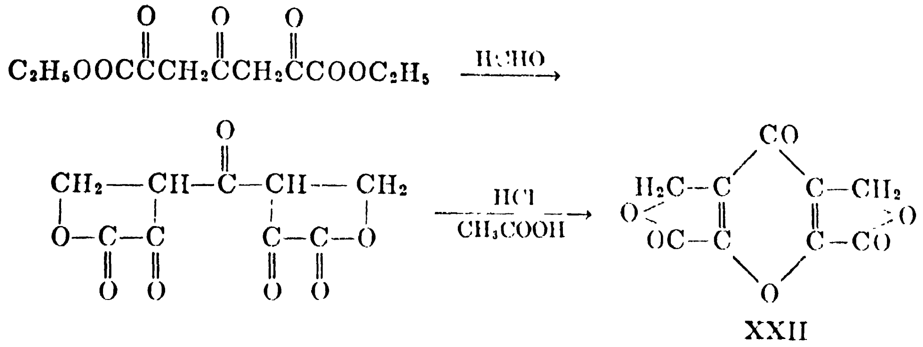
B

Clavacin and the isomer B are not mutually interconvertible by the action of either acids or heat.

Compounds related to clavacin: Various compounds related to clavacin have been synthesized (202), among them XXI and XXII. The reaction sequence is similar to that employed in the synthesis of compound B.



XXI



$$C_2H_5OOC\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}COOC_2H_5 \xrightarrow{HCHO}$$

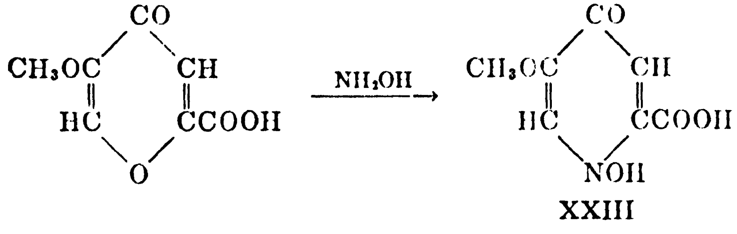
XXII

C. CHEMICAL PROPERTIES

1. *Reactivity of the carbonyl group*

The carbonyl group in the γ-pyrone nucleus exhibits an anomalous behavior. The reaction of γ-pyrones with reagents such as hydroxylamine and phenylhydrazine does not lead to the formation of the oxime or phenylhydrazone. This may be explained on the basis that γ-pyrones are not simple unsaturated ketones but are instead ester vinylogs $(-\overset{\overset{O}{\|}}{C}-C{=}C-O-)$ in which the carbonyl group has lost its activity as such and has taken on the characteristics of a carbonyl group present in an ester. The action of phenylhydrazine on 2,6-dimethylpyrone does not result in the formation of 2,6-dimethylpyrone phenylhydrazone (81). No known products have been isolated from this reaction.

The action of hydroxylamine on comenic (163), 6 hydroxycomenic, chelidonic, meconic (245), or pyromeconic (163) acids or their esters or on maltol (36) does not yield the oxime. In all cases the γ-pyrone nucleus remains intact. In the case of meconic acid the hydroxylamine salt is formed (192). The methyl ether of comenic acid yields an *N*-hydroxypyridone (XXIII) with hydroxylamine (195).

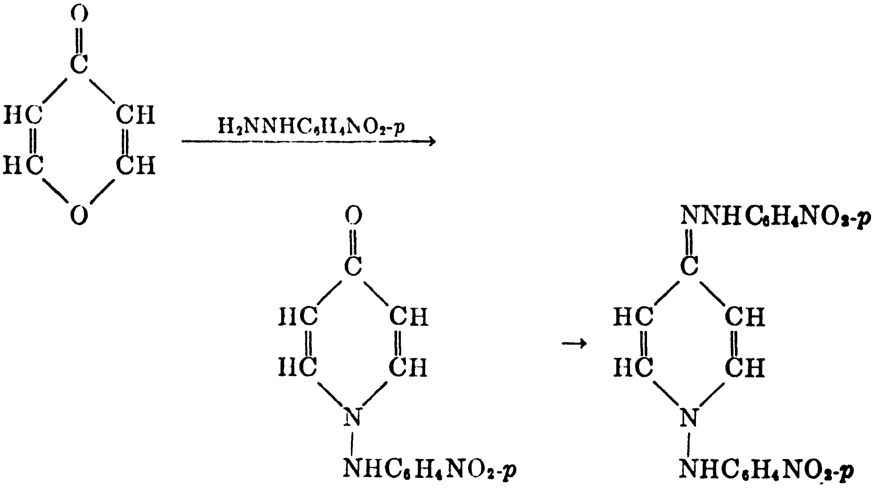


XXIII

This reaction is analogous to that encountered with ammonia.

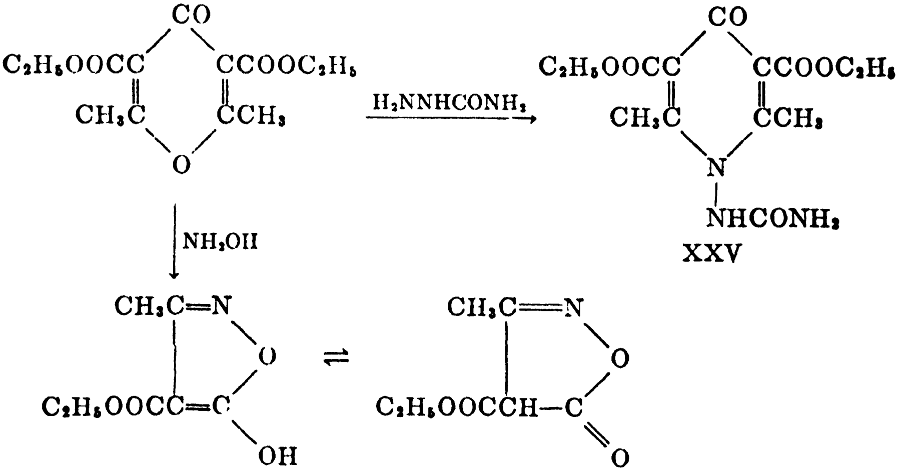
With the more reactive *p*-nitrophenylhydrazine, diethyl chelidonate and diethyl 3,5-dibromochelidonate react to give the *p*-nitrophenylhydrazones.

Under these conditions, γ-pyrone, chelidonic acid, and ethyl comanate produce the *p*-nitrophenylhydrazones of the *N*-*p*-nitrophenylamino-γ-pyridone.



XXIV

The action of semicarbazide on ethyl 2,6-dimethylpyrone-3,5-dicarboxylate produces an *N*-substituted γ-pyridone (XXV) (246). The reaction of hydroxylamine with ethyl 2,6-dimethylpyrone-3,5-dicarboxylate results in the formation of an isoxazalone (XXVI). The mechanism of this reaction is not clearly understood (170, 171).

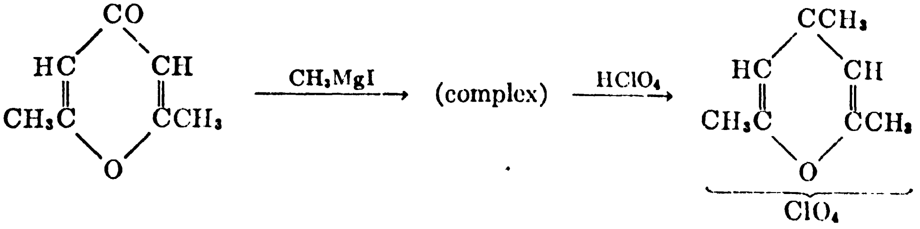


XXV

XXVI

The reaction between 2,6-dimethylpyrone and hydrazine produces a colorless liquid of unknown structure (131).

Grignard reagent: The action of methylmagnesium iodide on 2,6-dimethylpyrone produces a Grignard complex which yields 2,4,6-trimethylpyroxonium perchlorate when it is decomposed with perchloric acid (11). Phenylmagnesium bromide behaves in an analogous manner. Ammonia converts 2,4,6-trimethylpyroxonium perchlorate into 2,4,6-trimethylpyridine (collidine) (11).



2. *Behavior as α,β-unsaturated carbonyl compounds*

Reactions typical of α,β-unsaturated ketones do not occur with γ-pyrones. Thus, 2,6-dimethylpyrone does not react with malonic ester in the manner of the Michael condensation. The product of the reaction contains a molecule of 2,6-dimethylpyrone and a molecule of sodium malonic ester:

$$C_7H_8O_2 \cdot CHNa(COOC_2H_5)_2$$

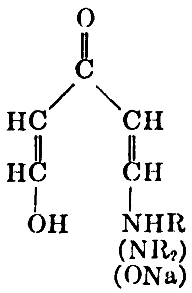
This salt-like addition compound is decomposed by water to yield a solution containing 2,6-dimethylpyrone and malonic ester (250).

The reaction of ammonia or amines to produce β-amino ketones does not occur in the pyrone series.

3. *Stability in alkaline and acid media*

(a) In alkaline solution

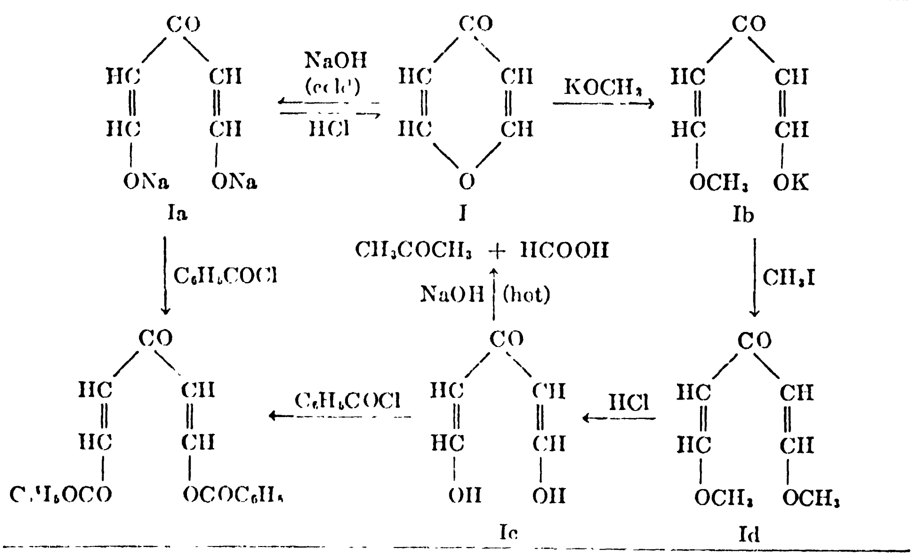
The action of bases on γ-pyrones causes cleavage of the ring. The ultimate product of this cleavage depends upon the nature of the base and the temperature of the reaction.



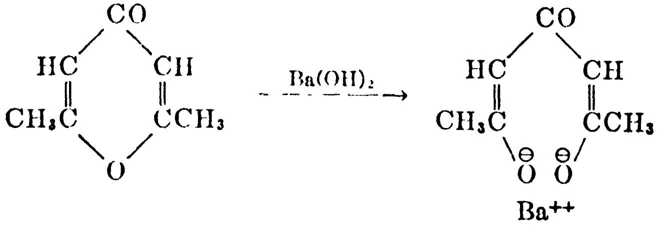
Alkali: The various reaction products obtained in alkaline media are shown in table 2 (261). γ-Pyrone is converted to the sodium salt of diformylacetone (Ia) by the action of cold sodium hydroxide. Diformylacetone dibenzoate may be formed by treating Ia with benzoyl chloride. Potassium methoxide cleaves γ-pyrone, producing the monomethyl ether of diformylacetone (Ib). The action of methyl iodide on Ib produces the dimethyl ether. The latter compound is hydrolyzed in acid solution with great ease. At elevated temperatures, the action of sodium hydroxide on γ-pyrone results in complete degradation, producing acetone and formic acid.

TABLE 2

Reactions of γ-pyrone under alkaline conditions



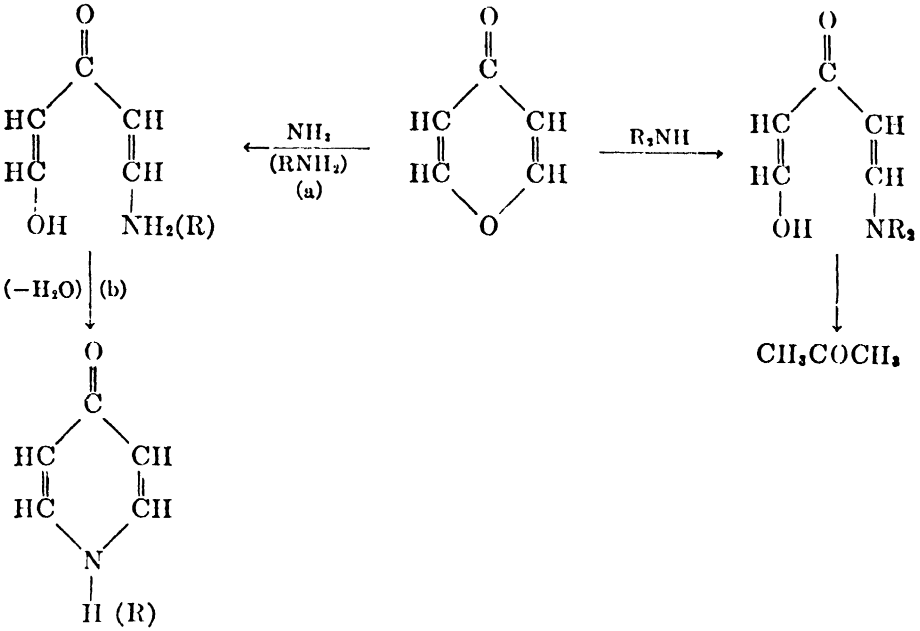
Barium hydroxide converts 2,6-dimethylpyrone into the barium salt of diacetylacetone (61).



Ammonia and amines: The γ-pyrone ring is transformed into a γ-pyridone ring by the action of ammonia (140, 168) and of primary amines (32, 65, 108, 171, 233).

Secondary amines cause the same type of cleavage; however, in this case cyclization (step b) cannot occur and the open-chain intermediate is hydrolyzed under the alkaline action of the dialkylamine.

The reaction to produce γ-pyridones is general with only a few exceptions. For example, the γ-pyrone nucleus in pyromeconic acid and maltol remains intact under the action of ammonia. In these cases an ammonium salt is formed. However, the methyl ethers of these compounds do react to yield the corresponding γ-pyridones (193, 194).



Potassium amide: The action of potassium amide (226) or 4-phenylbenzophenone potassium (225) on 2,6-dimethylpyrone produces a monopotassium salt.

(b) In acid solution

The γ-pyrone ring is stable in acid media. The only change which occurs involves the formation of pyroxonium salts (page 559).

4. Reduction

(a) Chemical reduction

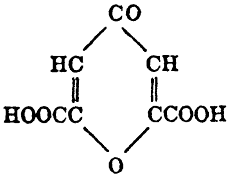
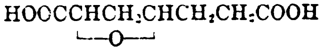
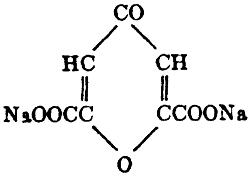
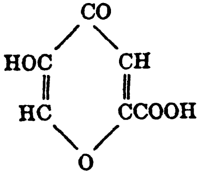
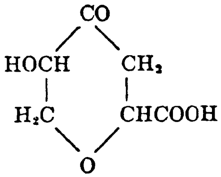
Reduction of the γ-pyrone ring by chemical means generally produces a complex reaction mixture. In some cases the ring is cleaved and aliphatic fragments result. This method is therefore not recommended for the preparation of tetrahydropyrones. Table 3 contains the known cases of chemical reduction.

(b) Catalytic hydrogenation

Catalytic hydrogenation affords a more successful method for the preparation of tetrahydropyrones than does chemical reduction. An outline of all the γ-pyrones that have been hydrogenated is contained in table 4.

TABLE 3

Chemical reduction of γ-pyrones

COMPOUND	REDUCING AGENT	PRODUCT	REFERENCE
 Chelidonic acid	Zn, CH_3COOH HI	 $\mathrm{HOOC\underbrace{CHCH_2CH}_{O}CH_2CH_2COOH}$	(81, 107, 141)
	Na(Hg)	$HOOCCHOHCH_2CHOHCH_2CHOHCOOH$	(107)
 Comenic acid	Na(Hg)		(135)

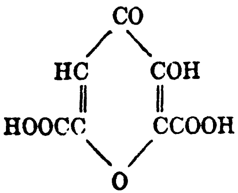
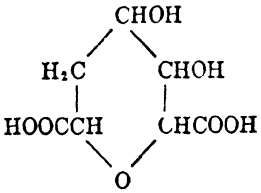
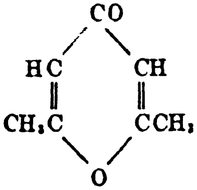
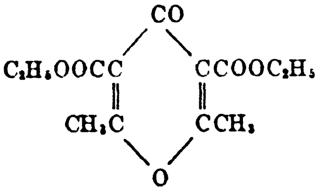
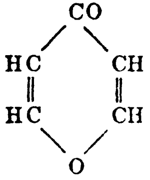
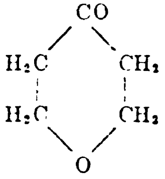
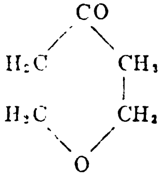
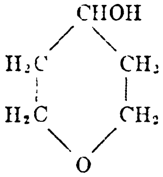
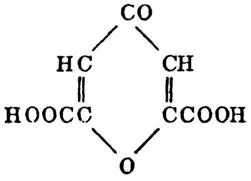
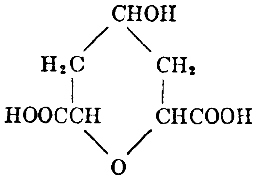
 Meconic acid	Na(Hg)		(135)
	Mg, CH_3COOH	Unidentified products	(12)
	Al(Hg) Na(Hg), CH_3COOH	No reduction Unidentified product	(246)

TABLE 4

*Catalytic hydrogenation of γ-pyrones**

COMPOUND	PRODUCT (PER CENT YIELD)	CATALYST	REFERENCE
 γ-Pyrone		$PdCl_2$	(30)
	 (23 per cent)  (50 per cent)	CuCrO	(160)†
 Chelidonic acid	No reduction	PtO_2	(156)
	 (97 per cent)	$Pd/BaSO_4$	(8)

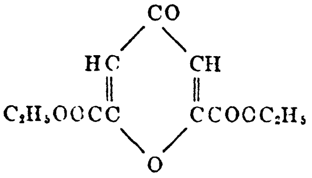
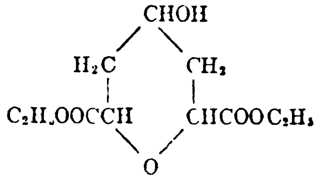
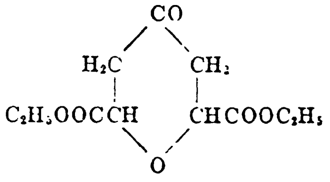
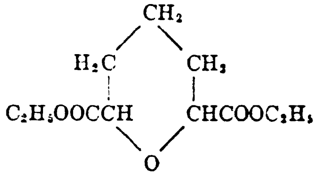
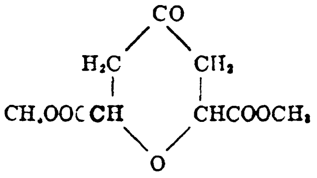
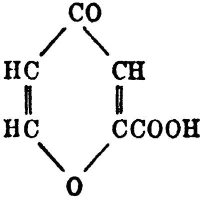
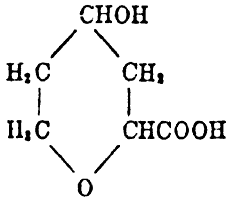
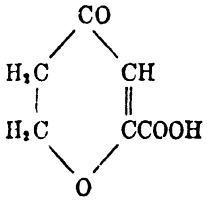
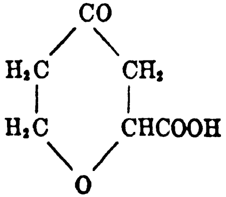
 Diethyl chelidonate	 (25 per cent)	Pd/BaSO$_4$	(8)
	 (9 per cent)	Raney nickel PtO$_2$ (alcohol) PdCl$_2$ (alcohol) Pd/BaSO$_4$	(8) (70) (30) (8)
		PtO$_2$ (CH$_3$COOH)	(69)
Dimethyl chelidonate	 (24 per cent)	Raney nickel	(8)

TABLE 4—*Continued*

COMPOUND	PRODUCT (PER CENT YIELD)	CATALYST	REFERENCE
 Comanic acid		Pd/BaSO$_4$	(8)
	 (14 per cent)	Pd/BaSO$_4$	(8)
	 (10 per cent)	Pd/BaSO$_4$ Pd/charcoal	(8)

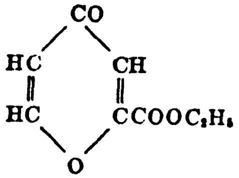
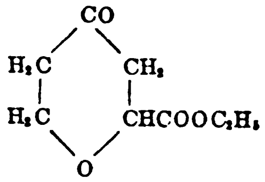
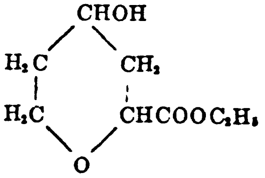
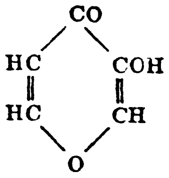
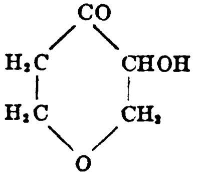
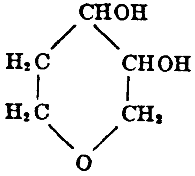
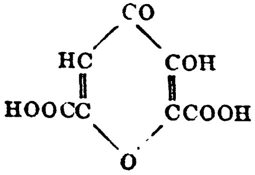
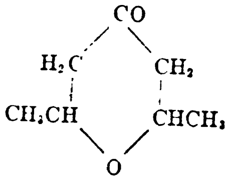
 Ethyl comanate	 (20 per cent)  (23 per cent)	Pd (colloidal)	(8)
 Pyromeconic acid	 	$PdCl_2$	(31)
 Meconic acid	$HOOCCHOHCHOHCHOHCH_2CHOHCOOH$	$PdCl_2$	

TABLE 1—*Continued*

COMPOUND	PRODUCT (PER CENT YIELD)	CATALYST	REFERENCE
2,6-Dimethylpyrone		PtO_2 $PdCl_2$	(70) (30)

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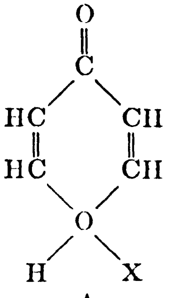
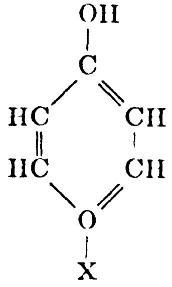
* All hydrogenations were carried out at room temperature and atmospheric pressure unless otherwise noted.

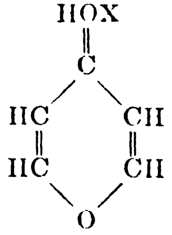
† High pressure, 125°C.

D. PYROXONIUM SALTS

The treatment of γ-pyrones with either organic or inorganic acids results in the formation of stable salt-like compounds which are known as pyroxonium salts. The structure of the pyroxonium salts has been the subject of wide discussion and at present no definite structure can be assigned to them. The major difficulty arises from the fact that there are two oxygen atoms present in the nucleus, each of which could theoretically participate in the salt formation.


A

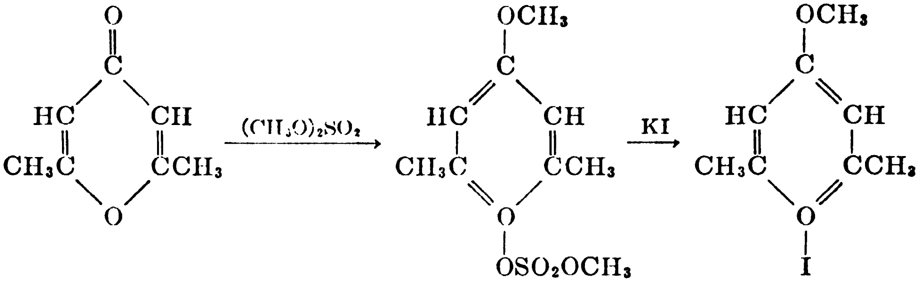

B


C

In the nitrogen system, structure A (a vinylogous tautomer of B) may be considered to be analogous to the acid salt of an amine (12, 13, 15, 51, 53, 54, 117), while structure C is equivalent to a ketimine hydrochloride. This analogy has served as the basis for the structure of the pyroxonium salts. Thus Hantzsch (111) has shown that freezing-point and conductivity measurements taken on a solution of 2,6-dimethylpyrone in concentrated sulfuric acid give rise to data similar to those observed on a system containing an amine and sulfuric acid. Further, the intense band in the ultraviolet region of the spectrum exhibited by 2,6-dimethylpyrone in alcohol is no longer evident when concentrated sulfuric acid is used as the solvent. This evidence has been interpreted as indicating the existence of structure B (256, 257). Gibbs, Johnson, and Hughes (96) reported that the ultraviolet absorption spectrum of 2,6-dimethylpyrone in alcohol is similar to that observed in alcohol containing an equivalent of hydrogen chloride. These workers suggested that the formation of pyroxonium salts does not involve any change in the structure of the γ-pyrone ring and proposed structure C. It is quite doubtful, however, that this solution is similar to that employing concentrated sulfuric acid as the solvent. At least part of the discrepancy may be due to the fact that 2,6-dimethylpyrone is a very weak base and the presence of only one equivalent of hydrogen chloride might not be sufficient to allow appreciable formation of pyroxonium salts.

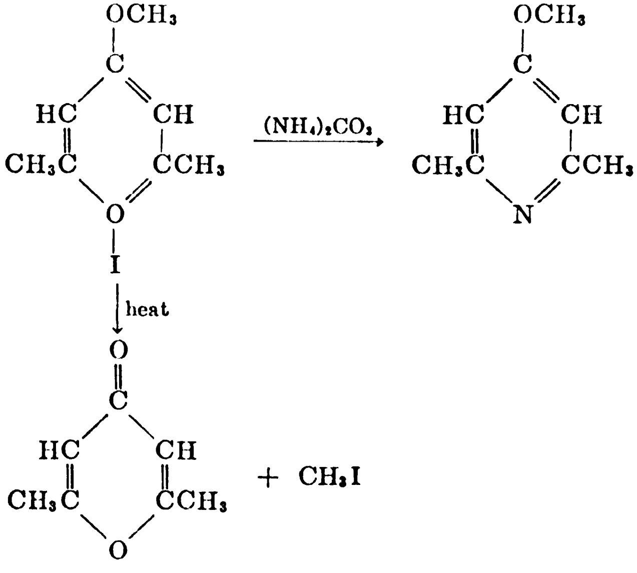
A more complex type of pyroxonium salt is one in which the ratio of acid to pyrone is not 1:1 (150). For example, Kendall (98, 127) isolated the following types of compounds from systems containing 2,6-dimethylpyrone and an organic acid: $C_7H_8O_2\cdot HX$, $2C_7H_8O_2\cdot 3HX$, $C_7H_8O_2\cdot 2HX$. The salts containing one molecule of pyrone for each molecule of acid were assigned structure C (173, 260), while the more complex salts were believed to involve the heterocyclic oxygen atom (148).

A second type of pyroxonium salt corresponds to the structure $(R_3O^+)\ X^-$. Kehrmann and Duttenhöfer (126) prepared this type by reacting 2,6-dimethylpyrone with methyl sulfate, followed by treatment with potassium iodide (97, 247).

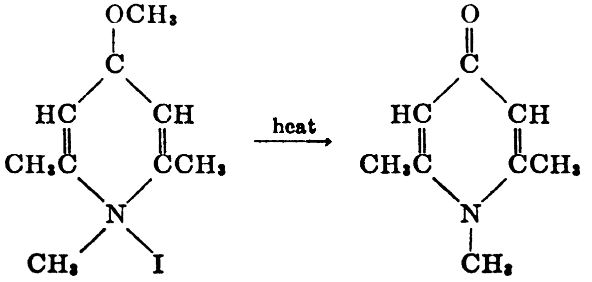


XXVII

Direct proof (10) of structure XXVII lies in the fact that it is converted to 2,6-dimethyl-4-methoxypyridine on treatment with ammonium carbonate. On heating, compound XXVII reverts to 2,6-dimethylpyrone and methyl iodide.



The latter reaction has a counterpart in the nitrogen system (63).



E. BASIC STRENGTH

Walker (255) and Wood (264) studied the rate of hydrolysis of methyl acetate in hydrochloric acid solution containing an equivalent of 2,6-dimethylpyrone. The velocity constant thus obtained was compared to that obtained from a solution of hydrochloric acid containing no 2,6-dimethylpyrone. The rate of hydrolysis was lower in the mixture containing 2,6-dimethylpyrone. They calculated 2,6-dimethylpyrone to be a stronger base than urea, and 2,3,5,6-tetramethylpyrone to be a weaker base than urea.

Using a similar point of attack, Johnson and Partington (122) and Mitchell and Partington (155) noted the decrease in the extent of esterification of phenylacetic acid in the presence of various γ-pyrones, using hydrochloric acid as the catalyst. It was concluded that this decrease was due to a combination between the γ-pyrone and the hydrochloric acid catalyst, an effect which would decrease the effective concentration of the hydrochloric acid. The retarding effect was found to be in the following decreasing order: 2,6-dimethylpyrone > 2-phenyl-6-methylpyrone > 2,6-diphenylpyrone > γ-pyrone. This interpretation overlooks the possibility that the pyroxonium ion may also contribute to the acid catalysis.

Rordam (216) approached the problem of the basicity of 2,6-dimethylpyrone from a different viewpoint. In an aqueous solution of 2,6-dimethylpyroxonium chloride the chloride-ion concentration is greater than the hydrogen-ion concentration if it is assumed that the unhydrolyzed pyroxonium salt dissociates into (2,6-dimethylpyrone)H$^+$ + Cl$^-$ (13).

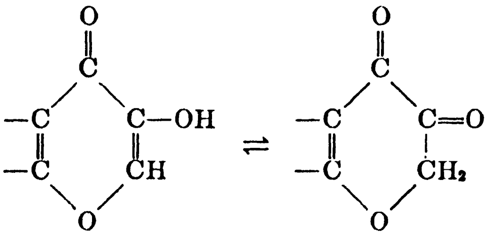
$$\text{2,6-Dimethylpyrone}\cdot\text{HCl} \xrightarrow{\text{hydrolysis}} \text{2,6-dimethylpyrone} + \text{H}^+ + \text{Cl}^-$$

$$\text{2,6-Dimethylpyrone}\cdot\text{HCl} \xrightarrow{\text{dissociation}} \text{2,6-dimethylpyrone}\cdot\text{H}^+ + \text{Cl}^-$$

Experimentally the chloride-ion concentration was found to be greater than the hydrogen-ion concentration. From his data, Rordam calculated the K_B for 2,6-dimethylpyrone to be 1.9×10^{-14} (254) (K_B for urea = 1.5×10^{-14}).

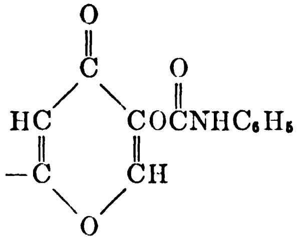
F. THE TAUTOMERISM OF HYDROXYPYRONES

The hydroxyl group in 3-hydroxypyrones is a component of a keto–enol tautomeric system. Evidence for the existence of this equilibrium is as follows:

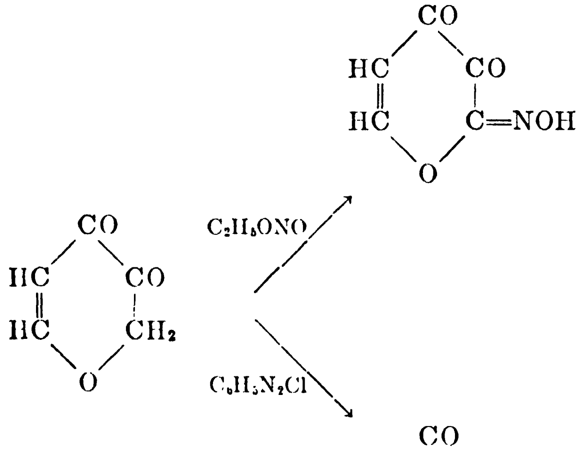


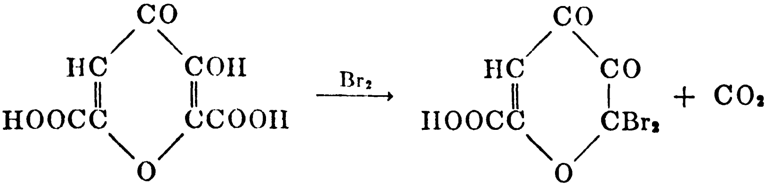
The reaction of hydroxypyrones with diazomethane yields the methyl ethers (188, 239, 245). Under the conditions of the Schotten–Baumann reaction a benzoate is formed (193). With acetic anhydride an acetate is produced (208).

The action of phenyl isocyanate results in the formation of a urethan (56). Hydroxypyrones develop a red coloration with ferric chloride.



Evidence for the keto form is seen in the following reactions (182):

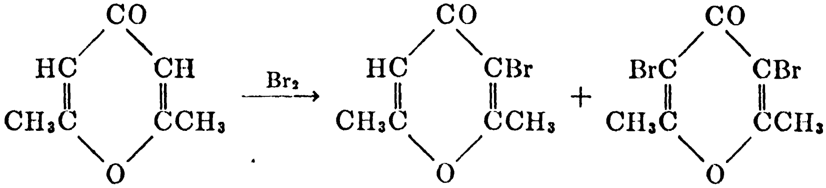


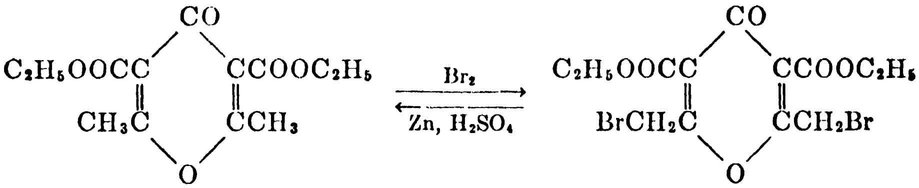


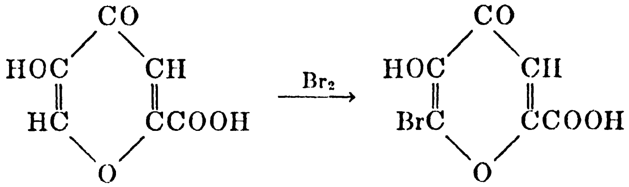
G. THE AROMATIC CHARACTER OF γ-PYRONES

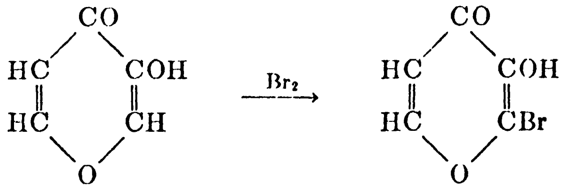
γ-Pyrones undergo several reactions which are typical of aromatic compounds. The reactions which will be considered are halogenation, mercuration, and nitration.

The pyrone nucleus exhibits a low degree of unsaturation toward halogens; substitution rather than addition occurs. For example, the action of bromine on 2,6-dimethylpyrone produces 3-bromo- and 3,5-dibromo-2,6-dimethylpyrones (56, 59, 86, 87, 88, 113). The bromination (or chlorination) of chelidonic acid yields 3,5-dibromochelidonic acid. Iodination of chelidonic acid under alkaline conditions results in the formation of 3,5-diiodochelidonic acid (140). When four groups are present in the pyrone nucleus, halogenation occurs in the side chain (172). Reduction of the bromo derivatives with zinc and sulfuric acid produces the starting compound. With hydroxypyrones bromination occurs on the carbon atom adjacent to the hydroxyl group (62, 183).

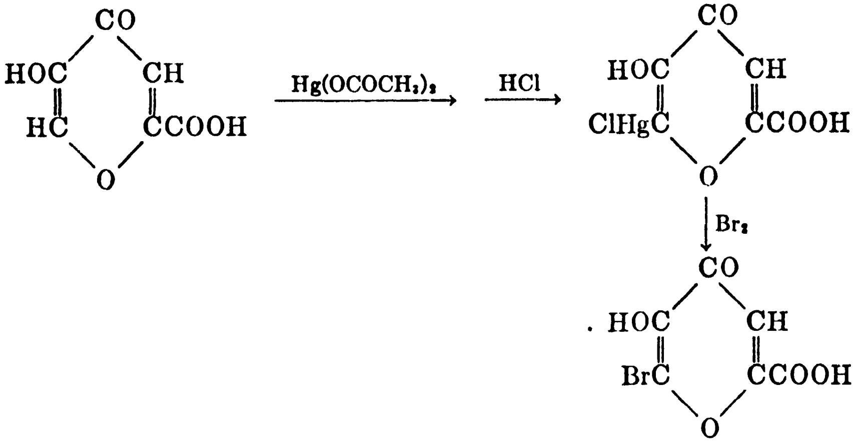




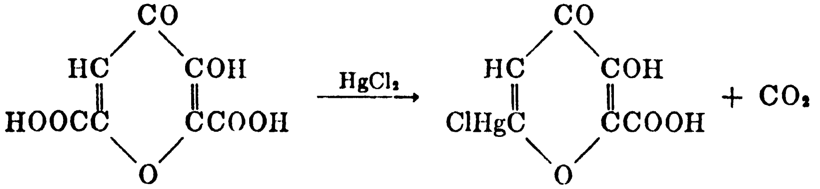




γ-Pyrones are mercurated in the same manner as aromatic compounds. For example, the action of mercuric acetate on comenic acid results in the formation of anhydro-6-mercuricomenic acid. Treatment of this compound with hydrochloric acid produces 6-chloromercuricomenic acid. The chloromercuri group is replaced by bromine (91).



6-Bromopyromeconic acid is prepared in a similar manner. Mercuration may also be accomplished by the use of mercuric chloride.

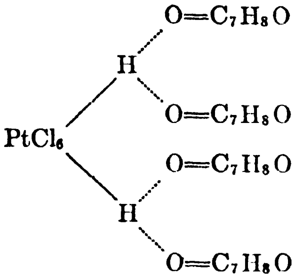


Nitration of the pyrone nucleus is carried out by employing fuming nitric acid as the nitrating agent (165, 208). Both comenic and pyromeconic acids yield a mononitro derivative in which the substituent is believed to be in position 6. Reduction with zinc and sulfuric acid produces the amino-γ-pyrone.

H. COMPLEX SALTS

A large number of complex salts have been prepared from 2,6-dimethylpyrone and heavy metal salts. Thus the reaction of zinc chloride and 2,6-dimethylpyrone results in the formation of a salt which contains one molecule of each component ($C_7H_8O_2 \cdot ZnCl_2$). In the presence of hydrochloric acid a zinc chloride hydrochloride ($C_7H_8O_2HCl \cdot ZnCl_2$) results (98). Mercuric chloride (257) or antimony chloride (151) yields similar compounds. A mixture of benzoyl chloride and antimony chloride produces $C_7H_8O_2 \cdot C_6H_5COCl \cdot SbCl_5$ (151).

Treatment of 2,6-dimethylpyrone with chloroplatinic acid produces a salt which contains two γ-pyrone ring residues (60). The structure of these complex salts has been discussed by Werner (257) and Morgan and Micklethwait (157). Werner proposed that the secondary valence forces of the carbonyl oxygen in the γ-pyrone ring are satisfied by the secondary valence forces of the hydrogen atoms in chloroplatinic acid.



III. α-PYRONES

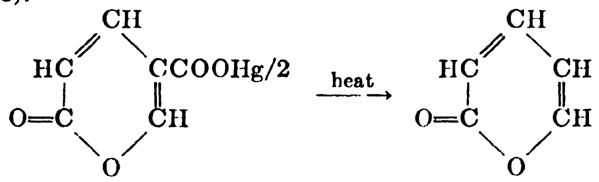
A. STRUCTURE

The α-pyrone ring possesses an unsaturated lactonic structure. The chemistry of the α-pyrones is not as complex as that of the γ-pyrones. Perhaps the most striking difference is that α-pyrones do not form pyroxonium salts with acids; however, the behavior toward alkaline reagents and halogens is similar.

B. PREPARATION

1. α-Pyrone (coumalin) (I)

Coumalin (I) may be prepared by the pyrolysis of the mercuric salt of coumalic acid (174, 175).



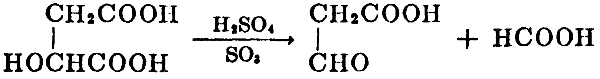
I

2. Substituted α-pyrones

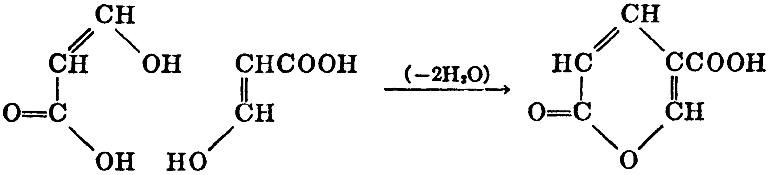
Substituted α-pyrones may be prepared by either condensation, cyclization, or rearrangement reactions or from pyrazolines. These reactions are briefly illustrated in table 5.

(a) By condensation

Coumalic acid: Coumalic acid (II) is formed by the action of fuming sulfuric acid on malic acid (174, 175). The intermediate in this reaction is formylacetic acid, which condenses as its enol form.



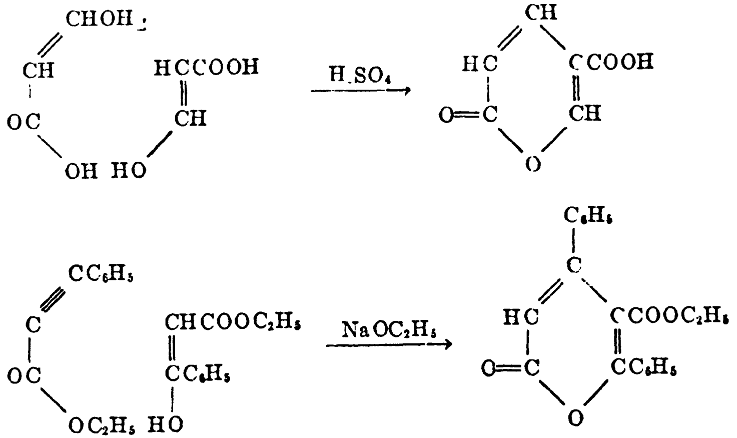
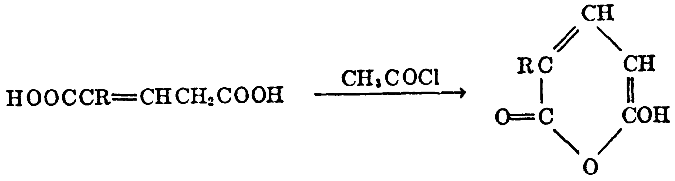
$$\begin{array}{l}CH_2COOH\\ |\\ HOCHCOOH\end{array} \xrightarrow[SO_3]{H_2SO_4} \begin{array}{l}CH_2COOH\\ |\\ CHO\end{array} + HCOOH$$

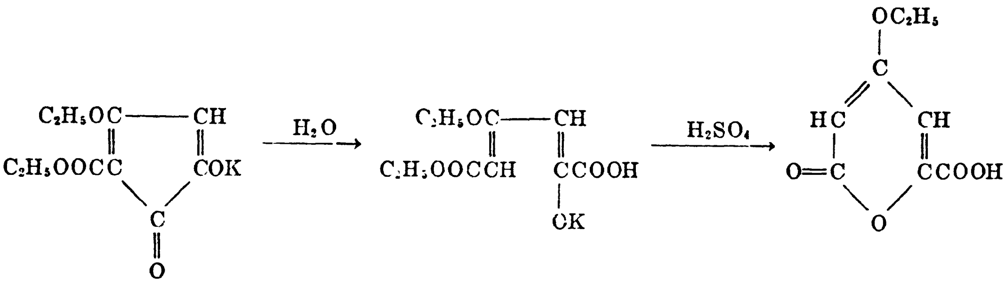
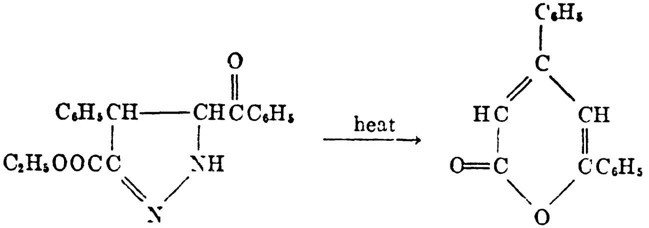


II

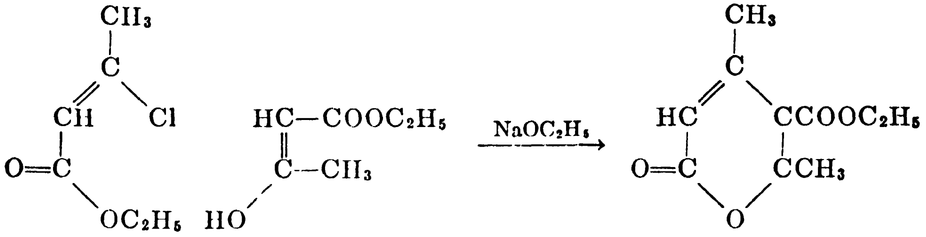
TABLE 5

Preparation of substituted α-pyrones

(*a*) Condensation	
(*b*) Cyclization	

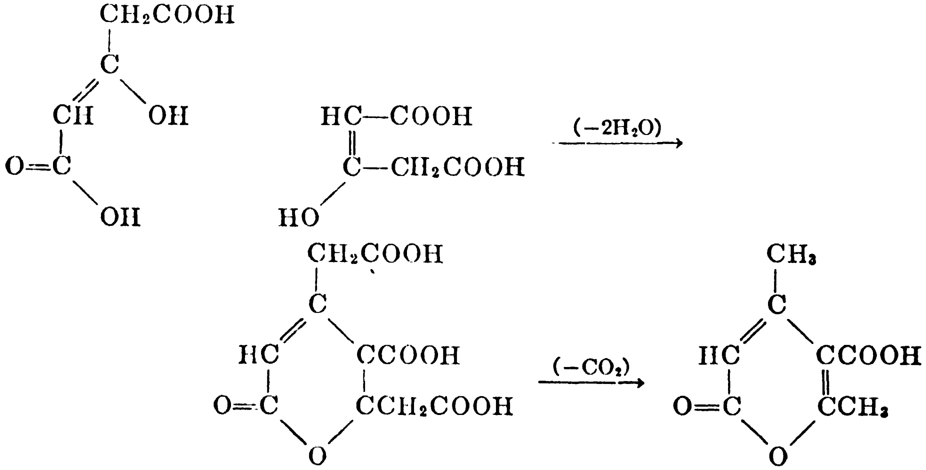
(*c*) Rearrangement................	
(*d*) From pyrazolines.............	

Isodehydroacetic acid: Isodehydroacetic acid (III) may be prepared either from ethyl acetoacetate and ethyl β-chlorocrotonate (2)



III

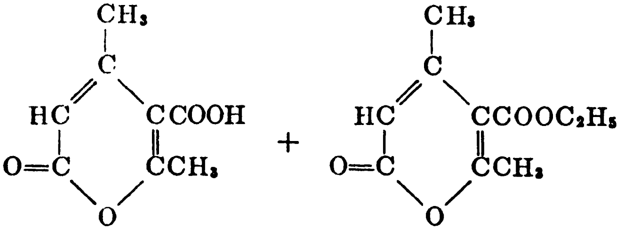
or by the action of fuming sulfuric acid on acetonedicarboxylic acid (162).



III

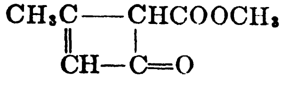
Decarboxylation of isodehydroacetic acid produces 4,6-dimethylcoumalin (2, 110). Isodehydroacetic acid is also obtained when acetoacetic ester is treated with concentrated sulfuric acid (110).

$$CH_3COCH_2COOC_2H_5 \xrightarrow{H_2SO_4} C_{18}H_{22}O_9 \xrightarrow{KOH}$$



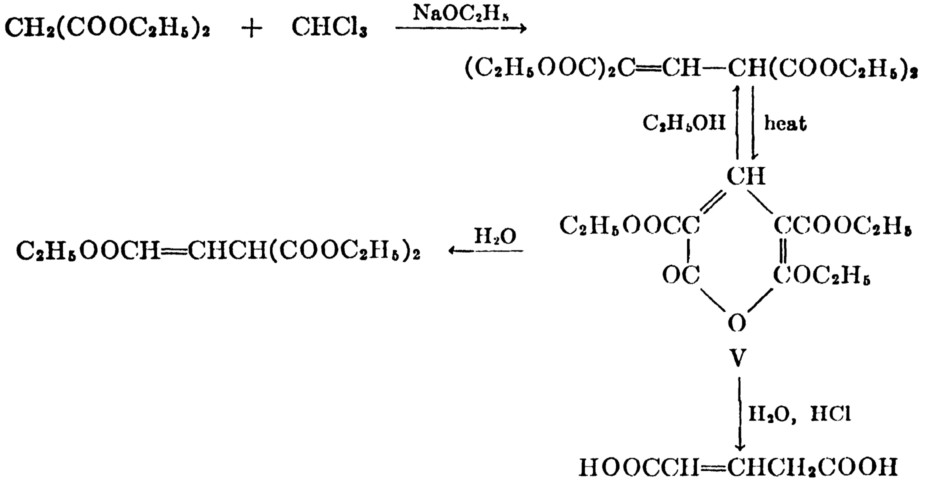
The structure of compound $C_{18}H_{22}O_9$ is unknown and the mechanism of the reaction is not understood.

The action of dry hydrogen chloride on acetoacetic ester produces a compound which is believed to be isodehydroacetic acid (76, 85, 199). However, evidence has been presented which indicates that the compound may have structure IV (95).

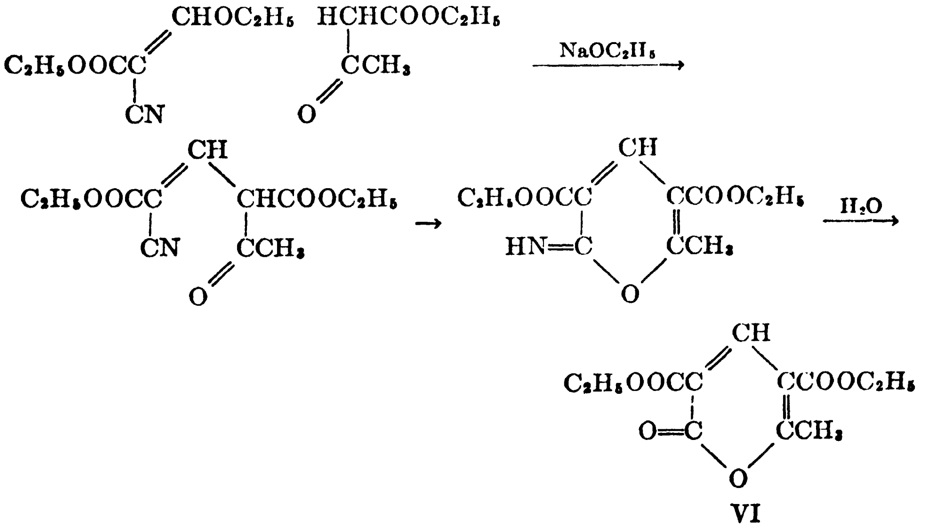


IV

Diethyl 6-ethoxycoumalin-3,5-dicarboxylate (V): The condensation of malonic ester with chloroform in the presence of sodium ethoxide results in the formation of compound V (102, 103). V undergoes both alcoholysis and hydrolysis with great ease. In the absence of hydrochloric acid V is partially saponified with subsequent decarboxylation; in the presence of acid, glutaconic acid is formed.



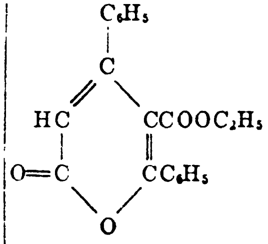
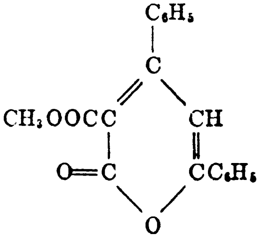
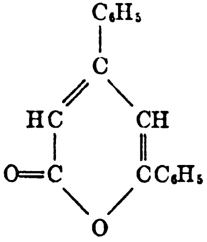
Diethyl 6-methylcoumalin-3,5-dicarboxylate (VI): VI is prepared in quantitative yield from ethyl ethoxymethylenecyanoacetate and ethyl acetoacetate.



VI

TABLE 6

Preparation of substituted α-pyrones by condensation

REACTANTS	CONDENSING AGENT	PRODUCT	REFERENCE
$C_6H_5C{\equiv}CCOOC_2H_5$ $C_6H_5COCH_2COOC_2H_5$	$NaOC_2H_5$		(218)
$CH_3OOCCH_2COOCH_3$ $C_6H_5C{\equiv}CCOC_6H_5$	$NaOC_2H_5$, then CH_3COOH		(132)
$C_6H_5COCH_2COOC_2H_5$	H_2SO_4 (concentrated)		(4)

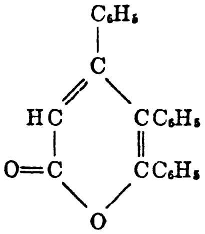
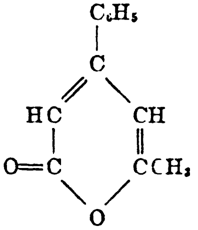
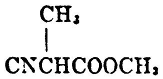
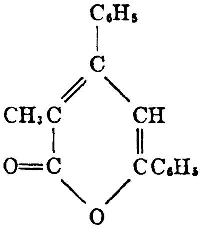
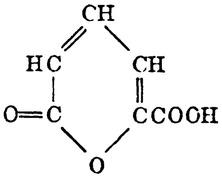
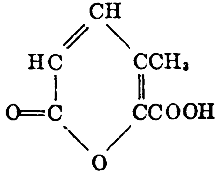
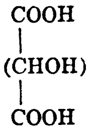
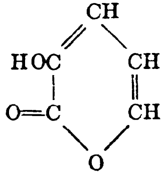
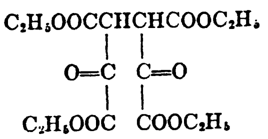
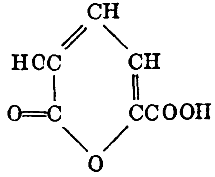
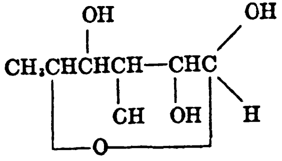
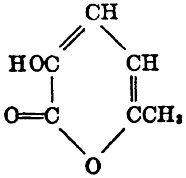
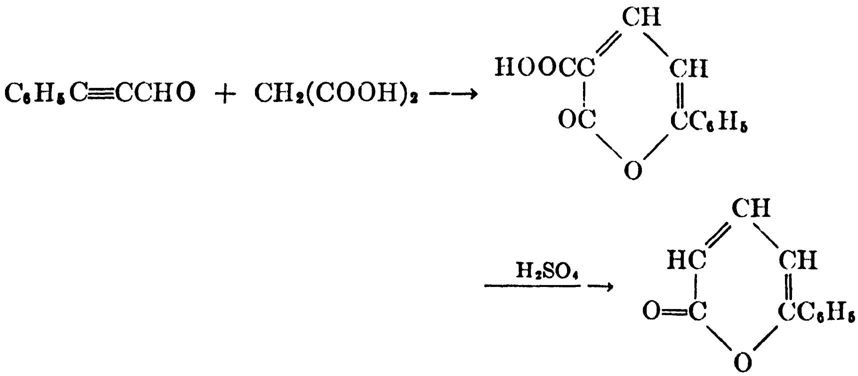
$C_6H_5C{\equiv}CCOOC_2H_5$ $C_6H_5COCH_2C_6H_5$	$NaOC_2H_5$		(220)
$C_6H_5{\equiv}CCOOC_2H_5$ $CH_3COCH_2COCH_3$	$NaOC_2H_5$		(221)
 $CN\overset{\overset{CH_3}{\vert}}{C}HCOOCH_3$ $C_6H_5C{\equiv}CCOC_6H_5$	$NaOCH_3$		(133)
$CH_3CH{=}CHCOOC_2H_5$ $(COOC_2H_5)_2$	$NaOC_2H_5$		(137, 200)

TABLE 6—*Continued*

REACTANTS	CONDENSING AGENT	PRODUCT	REFERENCE
$CH_3CH_2CH{=}CHCOOC_2H_5$ $(COOC_2H_5)_2$	$KOCH_3$		(93, 236, 258)
 $\begin{array}{c}COOH\\ \vert \\ (CHOH)_4\\ \vert \\ COOH\end{array}$	K_2SO_4, heat		(43, 43a, 44, 46, 230)
 $\begin{array}{l}C_2H_5OOCCHCHCOOC_2H_5\\ \qquad\quad \vert \quad\; \vert \\ \qquad O{=}C \;\; C{=}O\\ \qquad\quad \vert \quad\; \vert \\ \quad C_2H_5OOC \;\; COOC_2H_5\end{array}$	HCl		(25, 26)
	$KHSO_4$, heat		(230a, 252)

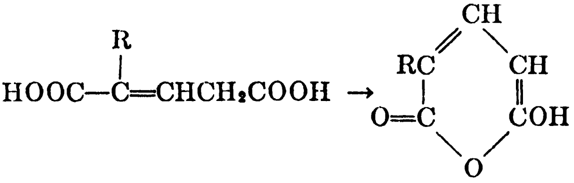
6-Phenylcoumalin: 6-Phenylcoumalin may be synthesized from phenylpropiolaldehyde and malonic acid (123). The mechanism of this reaction is not understood.



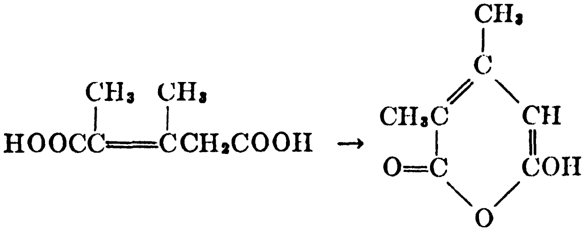
Other pyrones: In table 6 are listed other α-pyrones which may be prepared by condensation reactions.

(b) By cyclization

A large number of substituted α-pyrones have been prepared by cyclizing the the corresponding glutaconic acid derivatives (197, 240, 242). The following examples will serve to illustrate the generality of the method:



R = CH_3, C_6H_5, $C_6H_5CH_2$



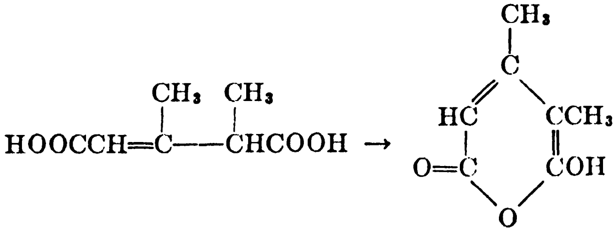
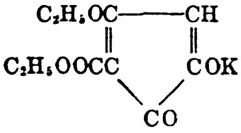
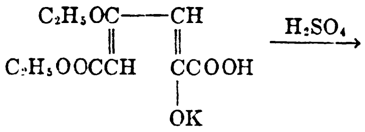
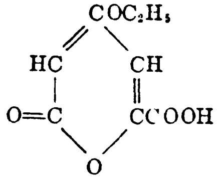
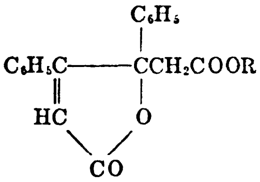
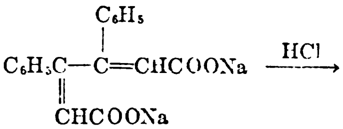
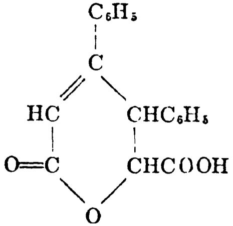
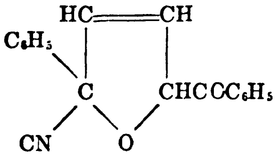
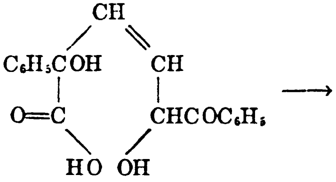
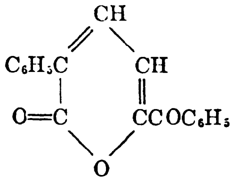
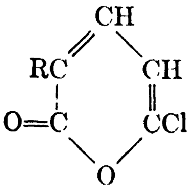


TABLE 7

Preparation of α-pyrones by rearrangement

STARTING COMPOUND	REAGENT	INTERMEDIATE	PRODUCT	REFERENCE
	H_2O			(262)
	Alcoholic NaOH			(23, 24)
	HCl, CH_3COOH			(94)

These cyclizations are effected by means of acetyl chloride at 100°C. In all cases the product is contaminated with the corresponding 6-chloro derivative.

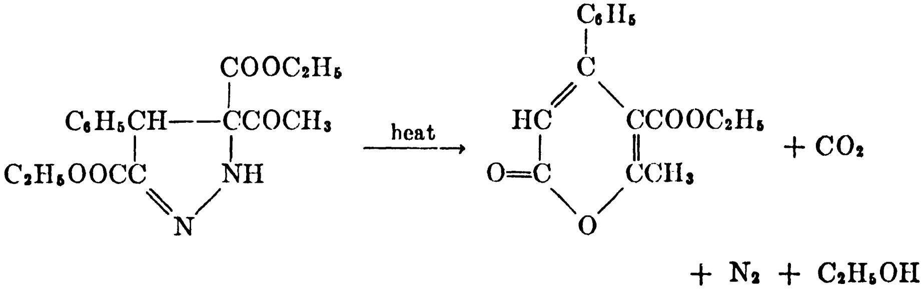


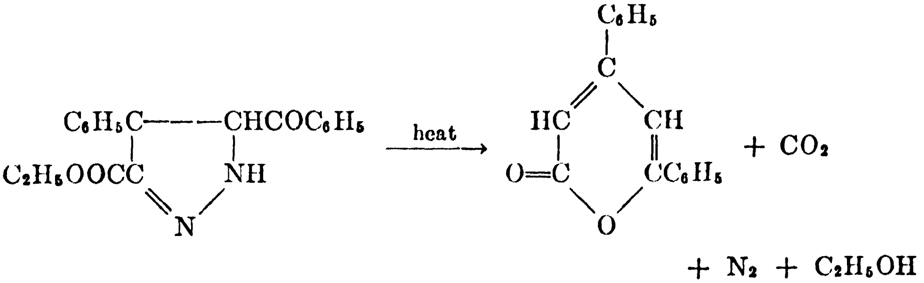
(c) By rearrangement

Rearrangements leading to the formation of substituted α-pyrones are listed in table 7.

(d) Coumalins from pyrazolines

Certain substituted pyrazolines may be converted to α-pyrones by heating (39, 134).



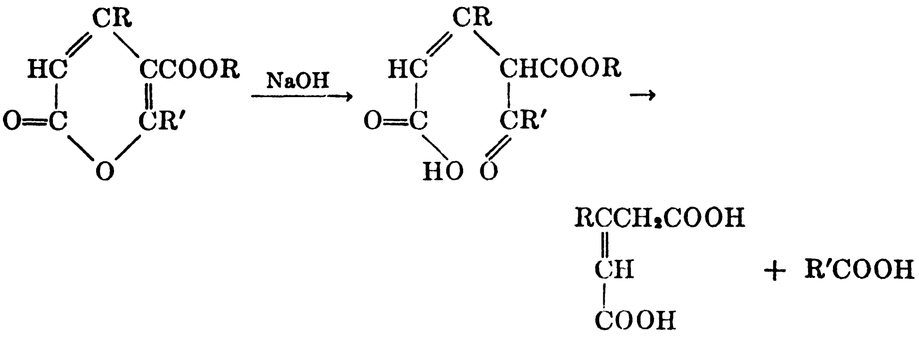


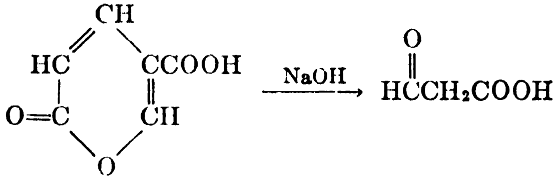
C. CHEMICAL PROPERTIES

1. *Action of bases*

(a) Alkali

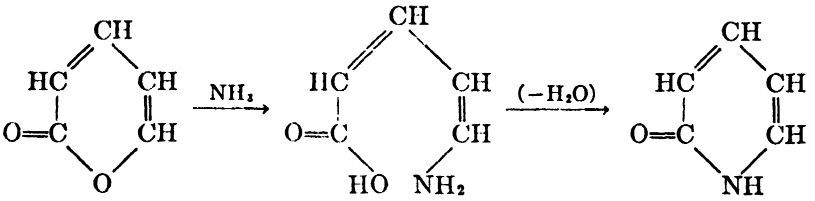
Alkali causes cleavage of the ring with subsequent hydrolysis of the cleavage product (27, 48, 49, 84, 102, 103, 132, 176, 229).



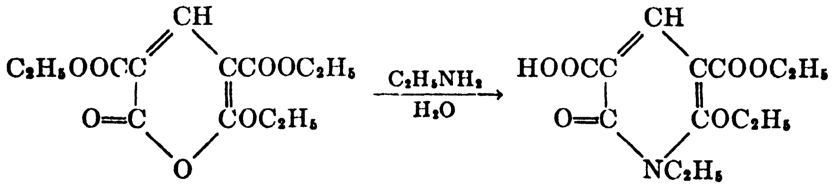


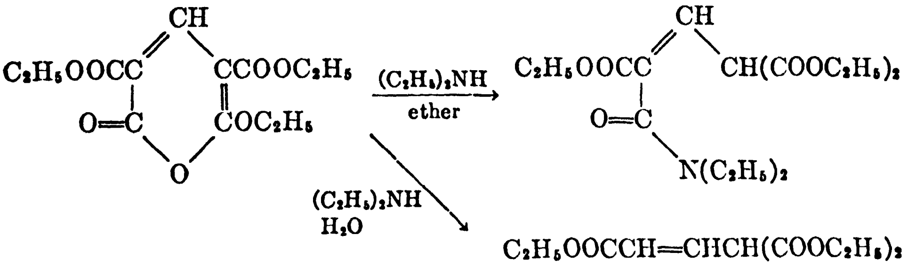
(b) Ammonia and amines

In general, the action of ammonia on α-pyrones produces α-pyridones (35, 80, 100, 128, 132, 149, 174, 175, 229). A similar type of reaction was observed in the γ-pyrone series. The mechanism for the formation of α-pyridones as proposed by Pechmann (179) is as follows:

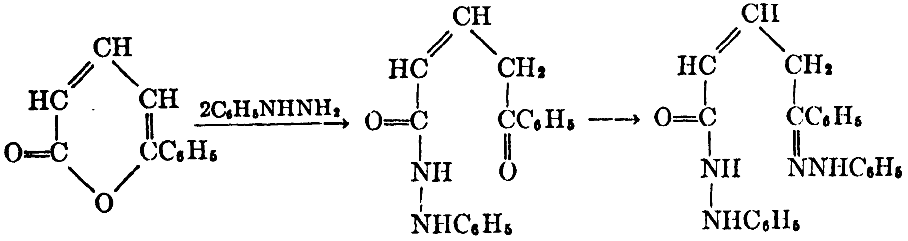


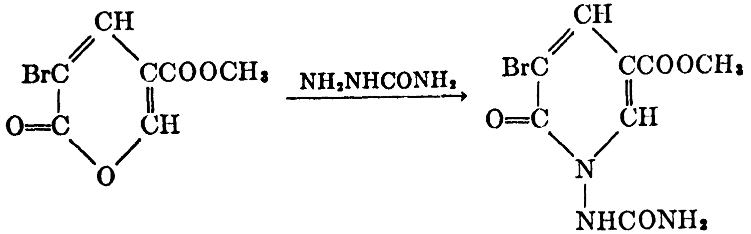
The action of primary amines results in the formation of *N*-substituted α-pyridones. Secondary amines cause cleavage of the ring, but cyclization of the cleavage product does not occur (16, 101, 104, 105, 114).





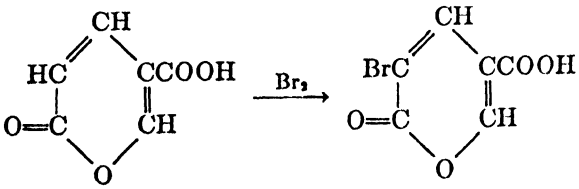
The action of phenylhydrazine or semicarbazide also causes cleavage of the α-pyrone ring (40, 43, 229). In the case of phenylhydrazine a phenylhydrazide is produced. With semicarbazide an *N*-substituted α-pyridone is formed.

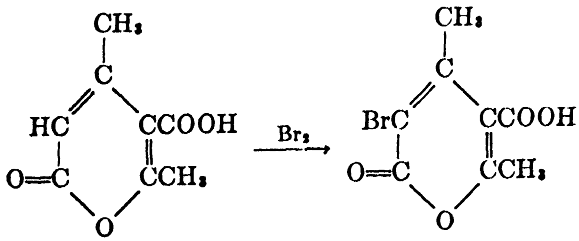




2. Halogenation

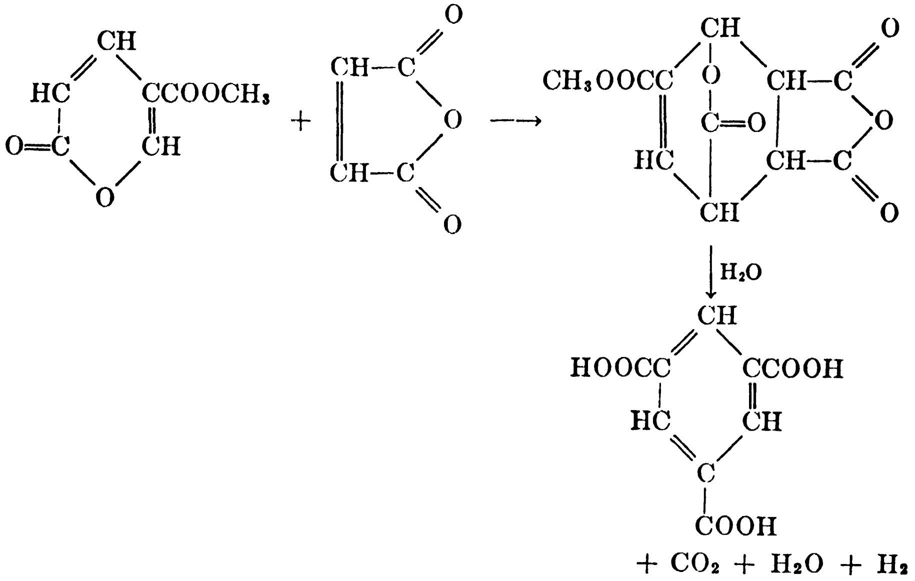
The action of bromine or chlorine on α-pyrones results in the formation of substitution rather than addition products (39, 45, 47, 83, 109, 175, 177, 178, 263).





3. The Diels–Alder reaction with α-pyrones

Diels and Alder (74) demonstrated that methyl coumalate undergoes the typical Diels–Alder reaction with maleic anhydride. It is interesting to note that hydrolysis of the addition product results in the formation of a benzene derivative.



The author is indebted to Dr. Marvin Carmack for many helpful criticisms and suggestions.

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THE α-KETO ACIDS

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A review of the known α-keto acids of the type formula $C_nH_{2n-2}O_3$ and those keto acids which may be considered the precursors of the naturally occurring α-amino acids is presented. Their general physical and chemical properties are discussed. Four methods which have been most successful in the preparation of the α-acids are illustrated. A table which lists references to the chemical methods for the preparation of the thirty-eight known α-keto acids which have been reported in the literature is given. Since pyruvic, hydroxypyruvic, oxaloacetic, and α-ketoglutaric acids are somewhat atypical and since they have received such extensive attention from investigators, it is thought that complete coverage of these four acids would be beyond the scope of this paper.

Berzelius (14) described the properties of pyruvic acid in 1835, and since then considerable interest has been shown in the α-keto acids. Biochemists have stressed the prevalence and the importance of these compounds. Westerkamp (135) isolated a number of the acids from the blood serum of horses and hogs. Neuberger and Sanger (110) indicated that the metabolism of lysine passes through its keto analog to glutaric acid, suggesting that a knowledge of keto acids is desirable for an understanding of amino acid metabolism. The interaction of amino acids with pyruvic acid has been proposed as a part of the biological mechanism of the inversion and acetylation of amino acids (45). Long and Peters (101) have observed that the rate of the decarboxylation of α-keto-*n*-valeric acid by yeast in the presence of essential carboxylase is increased by thiamine hydrochloride. The usefulness of the α-keto acids for synthetic purposes has been demonstrated by Bergmann and Grafe (13) and extended by Shemin and Herbst (127) to the synthesis of peptides. Kraft and Herbst (94) condensed carbamates with aliphatic aldehydes and with pyruvic acid to form compounds which were generally non-toxic and exerted some sedative and analgesic action in mice. Syntheses of α-amino acids from α-keto acids (90, 104) have also been proposed.

The increasing significance of this group of acids warrants a review, especially since they receive such meager treatment in organic treatises. Elementary textbooks usually dismiss the subject after a brief discussion of pyruvic acid, and some of the advanced texts do but little better. Richter (123) gives a description of five α-keto acids and outlines two general methods for their preparation. Some evidence of the voluminous literature on the α-keto acids is indicated by the fourteen and a half pages which the third edition of Beilstein devotes to pyruvic acid alone. The completed survey of phenylpyruvic acid yielded about one hundred and twenty references, including fourteen different procedures for its

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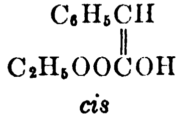
its preparation. Four of the α-keto acids,—namely, pyruvic, hydroxypyruvic, oxaloacetic, and α-ketoglutaric,—have received extensive attention from investigators. To summarize the methods of preparation and the reactions of these four acids would be beyond the scope of this paper. Since many of the chemical reactions and methods of preparation of the typical α-keto acids are not readily available from reference works on organic chemistry, it seemed desirable to review some of their reactions and to compile a list of the methods of preparation of the known α-keto acids. This information is summarized as follows: (I) A discussion of the general properties of the α-keto acids; (II) a discussion of the methods which have been found to be most general for their preparation; and (III) the presentation of a table which gives references to the preparation of the known α-keto acids of the type formula $C_nH_{2n-2}O_3$.

I. PROPERTIES OF THE α-KETO ACIDS

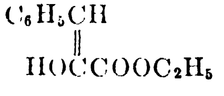
The branched-chain and the phenyl-substituted α-keto acids vary in physical characteristics from liquids to high-melting solids. The straight-chain α-keto acids are either liquids or low-melting solids. Adickes and Andresen (3) have pointed out that if the straight-chain α-keto acids, together with their melting points, are tabulated in two series according to whether the acids contain an odd or an even number of carbon atoms, it will be noted (*a*) that the melting points of the acids in each series increase as the molecular weights increase, and (*b*) that the difference between the melting points of any two successive members in either series becomes smaller with increasing length of the carbon chain. For example, an increase in the number of carbon atoms from five to seven increases the melting point 23°C., and an increase from six to eight carbon atoms increases the melting point 26°C.; an increase from seven to nine causes an increase of 14°C., and from eight to ten causes an increase of 14°C. It may also be observed that a keto acid has a higher melting point than the corresponding fatty acid. Table 1 serves to illustrate these observations.

Gault and Weicke (68) have shown that the ethyl ester of phenylpyruvic acid exists in three forms: the *cis-trans* enol forms, and the keto form.



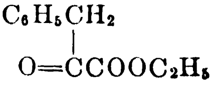
$$\begin{array}{c} C_6H_5CH \\ \| \\ C_2H_5OOCOH \end{array}$$

cis



$$\begin{array}{c} C_6H_5CH \\ \| \\ HOCCOOC_2H_5 \end{array}$$

trans



$$\begin{array}{c} C_6H_5CH_2 \\ | \\ O{=}CCOOC_2H_5 \end{array}$$

keto

Other α-keto acids capable of enolization also show this tendency (66, 67, 78).

Some α-keto acids are unstable on standing in the air; benzaldehyde, benzoic acid, and oxalic acid have been detected as decomposition products of phenylpyruvic acid (78). Their decomposition by microörganisms and by enzymes has been studied extensively; generally carbon dioxide and the lower alcohol or aldehyde are formed. Lead tetraacetate effects a quantitative evolution of carbon dioxide (7). Pyrolysis yields carbon dioxide, carbon monoxide, a lower aldehyde or acid, and dehydration products (86). Although the α-keto acids appear to be somewhat unstable, some show remarkable stability when heated with acids and bases. This is evidenced by the fact that many keto acids have been prepared by heating the immediate precursor in the synthesis with acid or alkali. A typical example of this is the preparation, described in *Organic Syntheses* (81), of phenylpyruvic acid by boiling α-acetaminocinnamic acid with 1 *N* hydrochloric acid for 3 hr.:

$$\mathrm{C_6H_5CH{=}C(NHCOCH_3)COOH + 2H_2O + HCl}$$
$$\rightarrow \mathrm{C_6H_5CH_2COCOOH + CH_3COOH + NH_4Cl}$$

Erlenmeyer's hydrolysis of phenylcyanopyruvic acid ester by heating for 12 hr. with dilute sulfuric acid (1 part acid to 2 parts water) to yield phenylpyruvic acid may also be mentioned (51):

$$\mathrm{C_6H_5CH(CN)COCOOC_2H_5} \xrightarrow{\text{dilute acid}} \mathrm{C_6H_5CH_2COCOOH}$$

However, Karrer (88) states that all known α-keto acids yield carbon monoxide when warmed with concentrated sulfuric acid.

TABLE 1

Melting points of straight-chain α-keto acids and of fatty acids

ODD			EVEN		
Number of carbon atoms	Melting point of α-keto acid	Melting point of fatty acid	Number of carbon atoms	Melting point of α-keto acid	Melting point of fatty acid
	°C.	°C.		°C.	°C.
3	14	−24	4	31	−5
5	6	−34	6	7	−1
7	29	−10	8	33	16
9	43	12	10	47	31
11	55	29	12	57	43
13	62	44	14	64	54
15	68	53	16	69	63

The α-keto acids generally form well-defined ketone derivatives. The oximes are usually stable compounds and are not easily reconverted to the original acids; these oximes are stable to alkali and with dilute acids lose carbon dioxide to form a nitrile with one less carbon atom (27, 134):

$$\mathrm{RC({=}NOH)COOH} \xrightarrow{\text{dilute acid}} \mathrm{RCN + CO_2 + H_2O}$$

With ferric chloride many α-keto acids develop characteristic colors. The acids may be titrated with bases; they form well-defined calcium, barium and silver salts. The sodium bisulfite addition compound of phenylpyruvic acid has been described (78). As a rule the acids reduce ammoniacal silver nitrate solution and are reduced by hydrogen to the corresponding hydroxy acid:

$$\mathrm{RCOCOOH} \xrightarrow{\mathrm{H_2}} \mathrm{RCHOHCOOH}$$

McKenzie (103) showed that α-keto acids which were esterified with an optically active alcohol could be reduced, in part at least, to an optically active α-hydroxy acid.

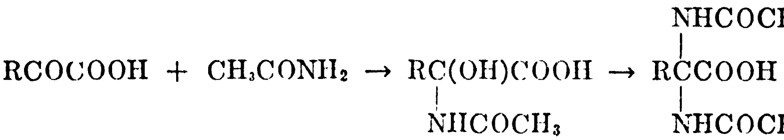
Knoop and Oesterlin (90) employed catalytic hydrogenation in the presence of mono- and of di-methylamine, respectively, to obtain several methylamino acids.

$$\mathrm{RCOCOOH + CH_3NH_2 \xrightarrow[catalyst]{H_2} RCH(NHCH_3)COOH}$$

Catalytic hydrogenation of keto acids in the presence of ammonia yields amino acids. Amino acids are also formed from the keto acids when the reaction with ammonia is catalyzed by ferrous sulfate or by cysteine (1, 91). When an α-keto acid is mixed with dog's blood containing ammonium salts, amino acids are obtained (47, 93). Transamination occurs when an amino acid is allowed to react with a keto acid, the amino acid forming a lower aldehyde (79, 80):

$$\mathrm{RCH(NH_2)COOH + R'COCOOH \rightarrow RCH(COOH)N{=}C(COOH)R'}$$
$$\mathrm{\rightarrow RC(COOH){=}NCH(COOH)R' \rightarrow RCHO + R'CH(NH_2)COOH}$$

The condensation of the α-keto acids with acetamide has been investigated by Shemin and Herbst (126). They state that the first reaction is the formation of an α-hydroxy-α-acetoamino acid; this then reacts with another molecule of acetamide, either directly or by dehydration followed by the addition of acetamide to the unsaturated intermediate.



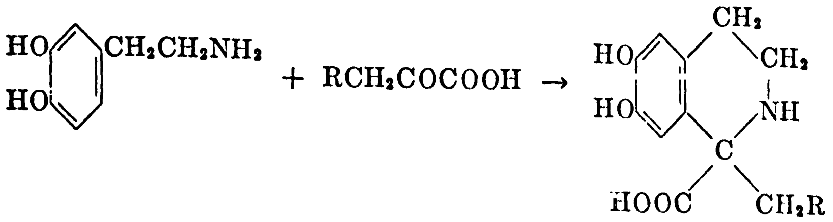
$$\mathrm{RCOCOOH + CH_3CONH_2 \rightarrow \underset{\displaystyle NHCOCH_3}{\underset{|}{RC(OH)COOH}} \rightarrow \overset{\displaystyle NHCOCH_3}{\overset{|}{\underset{\displaystyle NHCOCH_3}{\underset{|}{RCCOOH}}}}}$$

With benzoylformic acid the disubstituted derivative was isolated; with phenylpyruvic acid a molecule of water is apparently lost, with the formation of α-acetaminocinnamic acid; with α-ketoglutaric acid decarboxylation takes place with the formation of γ,γ-diacetaminobutyric acid. Shive and Shive (128) have condensed pyruvic acid with formamide to obtain α-hydroxy-α-formaminopropionic acid. Martell and Herbst (104) have condensed benzyl carbamate with α-keto acids to form a wide variety of products, depending upon the conditions employed. Catalytic hydrogenation of the dicarbamate condensation product constitutes a new method for the conversion of α-keto acids into α-amino acids:

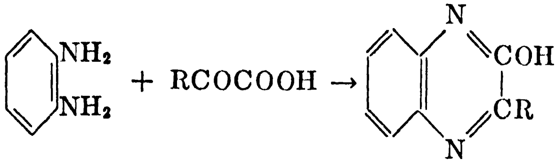
$$\mathrm{RCOCOOH + C_6H_5CH_2OCONH_2 \rightarrow RC(NHCOOCH_2C_6H_5)_2COOH}$$
$$\mathrm{\xrightarrow[catalyst]{H_2} RCH(NH_2)COOH}$$

Shemin and Herbst (127) have used the α-keto acids to prepare dipeptides.

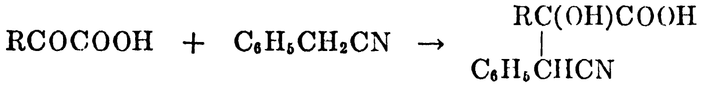
A number of investigators have condensed amines with the α-keto acids. Hahn and coworkers (72, 73, 74) have reported the reaction with tryptamine and have shown that those acids capable of enolizing react with the 3,4-dihydroxyphenethylamine derivatives to form the corresponding tetrahydroisoquinoline-1-carboxylic acids:



With *o*-phenylenediamine an α-keto acid effects ring closure to give a quinoxaline derivative (89):



In the presence of strong acids or alkalies the α-keto acids show a tendency to condense with themselves (34, 53, 56, 78). The condensation also takes place with aldehydes (50) and with ketones (38), following the aldol condensation pattern. Pyruvic acid (125) and phenylpyruvic acid (37) have been condensed with benzyl cyanide to form the corresponding cyanohydro derivative:



$$RCOCOOH + C_6H_5CH_2CN \rightarrow \begin{array}{c} RC(OH)COOH \\ | \\ C_6H_5CHCN \end{array}$$

It has been shown (119) that dimethylpyruvic acid reacts with benzene in the presence of concentrated sulfuric acid to form an addition product which is then dehydrated to β,β-dimethyl-α-phenylacrylic acid:

$$(CH_3)_2CHCOCOOH + C_6H_6 \rightarrow (CH_3)_2CHC(OH)(C_6H_5)COOH$$
$$\rightarrow (CH_3)_2C{=}C(C_6H_5)COOH$$

Toluene reacts with phenylpyruvic acid in the presence of cold concentrated sulfuric acid to form α,α-ditoluyl-β-phenylpropionic acid (15); ethylbenzene and xylene react similarly.

II. PREPARATION OF THE α-KETO ACIDS

Probably more α-keto acids have been prepared as oxidative degradation products in the course of proving the structure of a more complex compound than by any other method. Frequently special methods for preparing the individual acids are better than many of the so-called "general" methods. Notable among these are: the preparation of phenylpyruvic acid (81) and of benzoylformic acid (39) as described in *Organic Syntheses*; the preparation of pyruvic acid by the distillation of tartaric acid (84); and the preparation of hydroxypyruvic acid (102) by the breakdown of nitrocellulose. Krebs (95) developed a biological technique for the deamination of the α-amino acids by means of kidney slices, which has been used by a number of biological chemists for the preparation of the α-keto acids. Mild oxidation of the corresponding α-hydroxy acid, which is frequently mentioned as a method for preparing α-keto acids, does not seem to have been used extensively. Moureu *et al.* (107, 108) have recently succeeded in preparing keto acids from α,β-dibromo acids by forming an addition compound with piperidine and then hydrolyzing with dilute sulfuric acid. Four chemical methods are rather general for the preparation of α-keto acids. These are summarized briefly as follows:

A. Hydrolysis of the acyl cyanide

$$RCOX + MCN \rightarrow RCOCN \rightarrow RCOCOOH$$

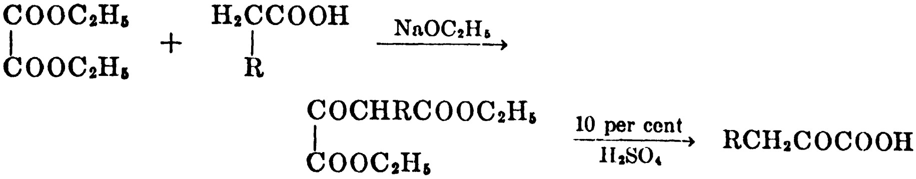
This method was first proposed by Claisen and Moritz (35) in 1880; they employed Hubner's (85) procedure, using silver cyanide to prepare the acyl cyanide. In 1929 Tschelinzeff and Schmidt (131) improved the procedure by substituting cuprous cyanide for silver cyanide. The acyl bromide and cuprous cyanide were warmed together on a water bath under reflux for about 2 hr. Yields of the acyl cyanide usually varied from 60 to 87 per cent. In the case of pyruvic acid and α-keto-*n*-butyric acid the hydrolysis of the cyanide was accomplished with cold concentrated hydrochloric acid and gave yields of about 75 per cent. In order to hydrolyze the isobutyl cyanide successfully, it was necessary to use dilute acid at room temperature. Neither Tschelinzeff and Schmidt (131) nor Claisen and Moritz (35) were able to hydrolyze isovaleryl cyanide. Many elementary and advanced textbooks in organic chemistry state that the hydrolysis of the acyl cyanides is a general procedure for preparing the α-keto acids. However, a survey of the literature indicates that the procedure has been employed only for the short-chain acids and it has been suggested (131) that the method is inapplicable for obtaining keto acids having more than five carbon atoms.

B. The hydrolysis of the oxime ester

$$RC({=}NOH)COOR' \xrightarrow[HOSO_2ONO]{\text{formic acid}} RCOCOOR' \rightarrow RCOCOOH$$

This method as orginally used by Bouveault and Locquin (26) in 1902 calls for 85 per cent formic acid and lead chamber crystals. Many variations of the method have been tried; however, no recent comprehensive study has been made. The best yields are probably obtained when the oxime is dissolved in 85 per cent formic acid, cooled to 0°C., and nitrosyl sulfuric acid added in small portions, with careful control of the temperature. Although yields of the order of 90 per cent have been reported for some of the acids, Adickes and Andresen (3) state that the conversion from the oxime to the keto acid is generally poor. Nevertheless this method has been more frequently used than any other for the general preparation of α-keto acids. Since compounds of the type $RC({=}NOH)COOH$ can be obtained in excellent yields from the substituted acetoacetic (77) and the substituted malonic esters (9), this method lends itself to the preparation of the α-keto acids. It has been reported that phenylpyruvic acid cannot be obtained from the oxime (76, 134); consequently it must not be assumed that the method is applicable to the preparation of all α-keto acids.

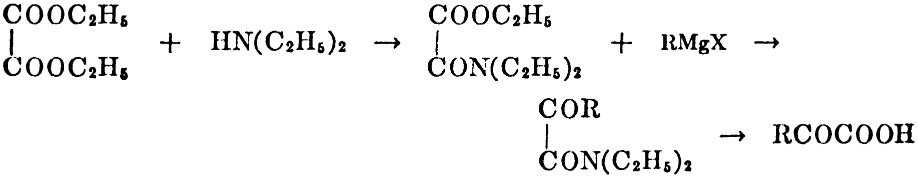
C. Hydrolysis of ethyl esters of oxalo acids



$$\begin{array}{l} COOC_2H_5 \\ | \\ COOC_2H_5 \end{array} + \begin{array}{l} H_2CCOOH \\ | \\ R \end{array} \xrightarrow{NaOC_2H_5} \begin{array}{l} COCHRCOOC_2H_5 \\ | \\ COOC_2H_5 \end{array} \xrightarrow[H_2SO_4]{10\text{ per cent}} RCH_2COCOOH$$

Adickes and Andresen (3) advanced this as a new method in 1943; however, Wislicenus (138) had suggested an analogous reaction using oxaloacetic ester in place of diethyl oxalate. Nine of the α-keto acids have been prepared by refluxing the fatty acid ester, diethyl oxalate, and sodium ethoxide in ether for about 16 hr. The keto acid was obtained by treating the isolated α-oxaloester with boiling dilute sulfuric acid for 6 hr. In order to prepare three of the longer chain acids (α-ketocapric, α-ketotridecanoic, and α-ketolauric) it was necessary to use potassium ethoxide in pyridine and heat for 100 hr. at 70°C. Yields of the purified α-keto acids varied from 8 to 94 per cent; however, yields of the crude product were considerably higher. This method is one of the most recent and probably the most general yet developed.

D. Hydrolysis of the addition product of Grignard reagents and diethyloxamates



$$\begin{array}{l} COOC_2H_5 \\ | \\ COOC_2H_5 \end{array} + HN(C_2H_5)_2 \rightarrow \begin{array}{l} COOC_2H_5 \\ | \\ CON(C_2H_5)_2 \end{array} + RMgX \rightarrow \begin{array}{l} COR \\ | \\ CON(C_2H_5)_2 \end{array} \rightarrow RCOCOOH$$

Barre (8) proposed this method in 1927 and showed its applicability in the preparation of four compounds. It would seem that the method should be very general; however, the condensation at −15°C. and the tediously long refluxing time requisite for the preparation of ethyl *N,N*-diethyloxamate have probably discouraged other investigators from extending the method. The author claimed 60 per cent yields and said that, when one considers the difficulties of the other methods for the preparation of α-keto acids, this method could be used to advantage.

III. ADDITIONAL INFORMATION ON α-KETO ACIDS

In table 2 is summarized part of the information which has been accumulated in the course of a literature survey. It is the purpose of the table to serve as a ready reference for anyone interested in preparing an α-keto acid. The melting points are given in a separate column, since they are not easily found in reference works. Where conflicting melting points have been reported, these are recorded. The data cover only the α-keto acids having the general formula $C_nH_{2n-2}O_3$, those

TABLE 2

Information on α-keto acids

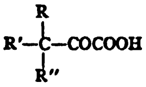
 $R'-\overset{R}{\underset{R''}{C}}-COCOOH$			MELTING POINT	FIRST PREPARED BY	GENERAL METHOD (AS DESCRIBED ABOVE)	REFERENCES TO OTHER METHODS OF PREPARATION
R	R′	R″				
			°C.			
H	H	H	13.6	Berzelius, 1835 (14)		Beilstein, Vol. III, p. 608
H	H	CH_3	31	Claisen and Moritz, 1880 (35)	A (35, 131) B (26, 99) C (139) D (8)	(5, 33, 40, 49, 52, 57, 63, 108, 120, 132, 140)
H	H	C_2H_5	6	Moritz, 1881 (106)	A (106) B (99) C (3)	(16, 58, 60)
H	CH_3	CH_3	31	Moritz, 1881 (106) Brunner, 1894 (29)	A (106, 131) C (121)	(2, 21, 25, 29, 42, 64, 70, 82, 92, 97, 114, 130)
H	H	n-C_3H_7	7	Kondo, 1912 (93)	B (93) C (3) D (8)	
H	H	i-C_3H_7	−1.5	Locquin, 1904 (99)	B (99) C (3)	(2, 36, 70, 115)
CH_3	CH_3	CH_3	125	Glucksmann, 1889 (69)		(4, 18, 19, 32, 122)
H	CH_3	C_2H_5	35	Mebus, 1905 (105) Bouveault and Locquin, 1905 (28)	B (28, 100) C (69)	
H	H	n-C_4H_9	52	Prezwalsky, 1913 (118)		
			29	Adickes and Andresen, 1943 (3)	C (3)	
H	H	i-C_4H_9	22	Fittig and Kaehlbrandt, 1899 (61)	B (99)	
CH_3	CH_3	C_2H_5	Liquid	Anschutz and Rauff, 1903 (4)		

TABLE 2—*Continued*

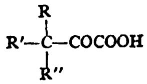
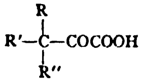
 $R'-\overset{R}{\underset{R''}{C}}-COCOOH$			MELTING POINT	FIRST PREPARED BY	GENERAL METHOD (AS DESCRIBED ABOVE)	REFERENCES TO OTHER METHODS OF PREPARATION
R	R'	R''	°C.			
H	H	n-C_5H_{11}	118	Smedley-MacLean and Pearce, 1934 (129)	B (129)	
			33	Adickes and Andresen, 1943 (3)	C (3)	
H	H	n-C_6H_{13}	106	Smedley-MacLean and Pearce, 1934 (129)	B (129)	
			43	Adickes and Andresen, 1943 (3)	C (3)	
H	H	n-C_7H_{15}	60	Smedley-MacLean and Pearce, 1934 (129)	B (129)	
			47	Adickes and Andresen, 1943 (3)	C (3)	
H	CH_3	n-C_6H_{13}	Liquid	Locquin, 1904 (99)	B (99)	
H	H	n-C_8H_{17}	55	Adickes and Andresen, 1943 (3)	C (3)	
H	i-C_4H_9	i-C_4H_9	Liquid	Freylon, 1910 (65)		
H	H	n-C_9H_{19}	57	Adickes and Andresen, 1943 (3)	C (3)	
H	H	n-$C_{10}H_{21}$	62	Adickes and Andresen, 1943 (3)	C (3)	
H	H	n-$C_{12}H_{25}$	68	Adickes and Andresen, 1943 (3)	C (3)	
H	H	n-$C_{13}H_{27}$	65	Kuwata, 1938 (98)	(6)	
			87	Darnstaedter and Lifschutz, 1896 (41)		
H	H	n-$C_{14}H_{29}$	83	Windaus and Van Schoor, 1926 (137)		
H	H	OH	Liquid	Wichelhaus, 1867 (136)		Beilstein, Vol. III, p. 869

TABLE 2—*Concluded*

 $R'-\overset{R}{\underset{R''}{C}}-COCOOH$			MELTING POINT	FIRST PREPARED BY	GENERAL METHOD (AS DESCRIBED ABOVE)	REFERENCES TO OTHER METHODS OF PREPARATION
R	R'	R''	°C.			
H	H	SH		Parrod, 1942 (112)		
H	OH	CH_3		Hoff-Jorgensen, 1940 (83)		
H	H	CH_3SCH_2		Waelsch and Borek, 1939 (113)		(30, 113)
H	H	COOH	176	Fenton and Jones, 1900 (55)		Beilstein, Vol. III, p. 777
H	H	CH_2COOH	113	Blaise and Gault, 1908 (17)		Beilstein, Vol. III, p. 789
H	H	C_6H_5	153	Plochl, 1883 (116)	C (138) D (8)	(12, 22, 23, 24, 43, 44, 48, 49, 51, 81, 107, 124)
H	H	2-HOC_6H_4	153	Plochl and Wolfrum, 1885 (117)		(58, 62)
H	H	3-HOC_6H_4	165	Flatow, 1910 (62)		(75)
H	H	4-HOC_6H_4	220	Neubauer, 1909 (109)		(12)
H	H	$NH_2(CH_2)_3$	103	Wolffenstein, 1893 (111)		(Author in doubt as to exact formula)
H	H	$NH_2(CH_2)_2$		Krebs, 1939 (96)		
H	H	Imidazolyl		Novello, Harrow, and Sherwin, 1926 (111)		
H	H	β-Indolyl	212	Ellinger and Matsuoka, 1920 (46)		(10, 11, 20, 70, 87)
Thyroxine analog			173	Canzanelli, Guild, and Harington, 1935 (31)		

acids which can be considered as precursors of the naturally occurring α-amino acids, and a few acids which were noted in the course of the survey.

The acids are classified as derivatives of pyruvic acid. In the fourth column, under "general method," the letters A, B, C, and D refer to the four general methods, respectively, discussed above. In the last column are given literature references to other methods of synthesis. Beilstein references are given for the four acids on which the survey is incomplete. References to the numerous chemical and biological reactions of the α-keto acids are not included in the table.

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